UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 16-DEC-2009

SUBJECT: Flutriafol. **REVISED** Human-Health Risk Assessment for Proposed Uses on Apple and Soybean.

PC Code: 128940
Decision No.: 377412
Petition No.: 7F7197
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D372347
Registration No.: 67760-TL, 4787-LL
Regulatory Action: Section 3 Registration
Case No.: NA
CAS No.: 76674-21-0
40 CFR: §180.629

FROM: Kelly M. Lowe, Environmental Scientist
Thomas Bloem, Chemist
William Greear, M.P.H., D.A.B.T., Toxicologist
Robert Mitkus, Ph.D., D.A.B.T., Toxicologist
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED) (7509P)

Gregory Akerman, Ph.D., Toxicologist
Elizabeth Mendez, Ph.D., Toxicologist
Toxicology and Epidemiology Branch (TEB), HED (7509P)

THRU: Dana M. Vogel, Branch Chief
George F. Kramer, Ph.D., Senior Chemist
RAB1, HED (7509P)

Jess Rowland, Toxicologist
Dennis McNeilly, Chemist
Risk Assessment Review Committee (RARC) Secondary Review

TO: Mary Waller, Risk Manager 21
Registration Division (RD; 7505P)

Note: This document supersedes the previous flutriafol human-health risk assessment (Memo, 01-JUN-2009, K. Lowe, *et al.*, D353078).

Under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, Cheminova has requested registration of the fungicide flutriafol. The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure

data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed uses of flutriafol in/on apple and soybean.

A summary of the findings and an assessment of human-health risk resulting from the proposed and registered uses of flutriafol are provided in this document. The residue chemistry review and dietary-exposure assessment was provided by Thomas Bloem (RAB1); the hazard and dose-response assessment was provided by William Greear (RAB1), Gregory Akerman (TEB), Elizabeth Mendez (TEB) and Robert Mitkus (RAB1); the occupational/residential exposure assessment and the risk assessment were provided by Kelly Lowe (RAB1); and the drinking water assessment was provided by Lucy Shanaman of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Flutriafol ((±)-α-(2-fluorophenyl)-α-(4-fluorophenyl)-1*H*-1,2,4-triazole-1-ethanol) is a systemic, triazole fungicide that can be used as a systemic eradicant and a protectant. It has a post-infection activity that can stop pathogen establishment in the early phases of disease development. There are no Section 3 uses or permanent tolerances currently established for flutriafol. Furthermore, there are no registered or proposed uses of flutriafol that would result in residential exposure. The last HED risk assessment for flutriafol was performed in 2006 (Memo, J. Tyler, D319153, 3/30/2006) for a Section 18 Emergency Exemption for use on soybean (time-limited tolerance of 0.1 ppm; 40 CFR 180.629).

Proposed Uses
For the current action, Cheminova proposes new food/feed uses of flutriafol on apples and soybeans. The application rate is 0.11 pounds (lb) active ingredient (ai)/acre (A) for both apples and soybeans. The maximum seasonal use rate is 0.63 lb ai/A for apples and 0.23 lb ai/A for soybeans. The specified minimum retreatment interval (RTI) for apples is 7-14 days and for soybeans is 14-35 days. The pre-harvest interval (PHI) for apples is 14 days and for soybeans is 21 days. Based on the proposed uses, dietary and occupational exposures are expected.

Hazard Characterization
Flutriafol has low acute oral toxicity and low acute inhalation toxicity. There is no acceptable acute dermal toxicity study in the database; however, a 28-day dermal toxicity study did not reveal any signs of toxicity at the limit dose (1000 mg/kg/day). Therefore, based on this study, flutriafol is classified in Category II for acute toxicity. Flutriafol is minimally irritating to the eyes (Toxicity Category III) and is not a dermal irritant (Toxicity Category IV). Flutriafol was not shown to be a skin sensitizer when tested in guinea pigs.

Flutriafol appears to be generally equally toxic to rats, mice, and dogs with all three species having similar (within one order of magnitude) no-observed adverse-effect levels (NOAELs)/lowest-observed adverse-effect levels (LOAELs). The target organ is the liver in dogs, rats, and mice. Hepatotoxicity occurred at similar dose levels across several species and durations of exposure. Flutriafol is considered to be "Not likely to be Carcinogenic to Humans" based on the results of the carcinogenicity studies in rats and mice. The results of the rat chronic toxicity/carcinogenicity study and the mouse carcinogenicity study are negative for carcinogenicity. All genotoxicity studies on flutriafol showed no evidence of clastogenicity or mutagenicity.

The potential impact of *in utero* and perinatal flutriafol exposure was investigated in three developmental toxicity studies (two in rats, one in rabbits) and a multigeneration reproduction toxicity study in rats. Only one of the rat developmental toxicity studies was acceptable. In the acceptable rat developmental study, a qualitative susceptibility was noted. Although developmental toxicity occurred at the same dose level that elicited maternal toxicity, the developmental effects were more severe than those observed in the dams. For rabbits, intrauterine deaths occurred at a dose level that also caused adverse effects in maternal animals. Similar to what was seen in the developmental study in rats, offspring effects occurred at the same dose level as parental effects in the multi-generation toxicity study in rats. However, the nature of the effects in the offspring was more severe than in the dams. Clear NOAELs were observed in all of these studies. Signs of neurotoxicity were reported in the acute and subchronic neurotoxicity studies at the highest dose only; however, these effects were primarily seen in

animals that were agonal (at the point of death) and, thus are not indicative of neurotoxicity. In addition, there was no evidence of neurotoxicity in any additional short-term studies in rats, mice, and dogs, or in the long-term toxicity studies in rats, mice, and dogs. A developmental-neurotoxicity (DNT) study is not required.

An *in vivo* rat dermal-absorption study is available for flutriafol that is acceptable and indicates that the absorption is 17%, 21%, and 11%, respectively, at 2, 20, and 200 µg/cm^2, following a 10-hour exposure. A conservative dermal-absorption value of 21% absorption is considered appropriate for dermal risk assessments. There is an absence of systemic toxicity at 1000 mg/kg/day in the 28-day dermal toxicity study in the rat.

Food Quality Protection Act (FQPA)
The flutriafol risk assessment team recommends that the 10X FQPA Safety Factor (SF) be reduced to 1X since the toxicology database is complete, there are no residual uncertainties for pre and/or post natal toxicity, and the conservative nature of the dietary exposure analysis (i.e., tolerance-level residues and 100% crop treated; no residential uses).

Dose-Response Assessment
The acute dietary points of departure for child-bearing females (13+ years old) was based on the prenatal developmental toxicity study in rabbits, where the LOAEL was 15 mg/kg/day [based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss] and the NOAEL was 7.5 mg/kg/day. An uncertainty factor (UF) of 100X (10-fold for interspecies extrapolation and 10-fold for intra-species variability) was applied to the NOAEL of 7.5 mg/kg/day to derive the acute reference (aRfD) dose for child-bearing females (13+ years old). The FQPA SF of 1X is applicable for acute dietary risk assessment for females 13+ years old. Therefore, the acute population-adjusted dose (aPAD) for females 13+ years old is 0.075 mg/kg/day.

The acute dietary point of departure for the general population was based on the acute neurotoxicity screening battery in the rat, where the LOAEL was 750 mg/kg/day (based on decreased body weight, body-weight gain, absolute and relative food consumption, and clinical signs of toxicity in both sexes: dehydration, urine-stained abdominal fur, ungroomed coat, ptosis, decreased motor activity, prostration, limp muscle tone, muscle flaccidity, hypothermia, hunched posture, impaired or lost righting reflex, scant feces; in males: red or tan perioral substance, chromodacryorrhea, chromorhinorrhea and labored breathing, and in females: piloerection and bradypnea) and the NOAEL was 250 mg/kg/day. An UF of 100X (10-fold for interspecies extrapolation and 10-fold for intra-species variability) was applied to the NOAEL of 250 mg/kg/day to derive the aRfD. The FQPA SF of 1X is applicable for acute dietary risk assessment. Therefore, the aPAD for the general population is 2.5 mg/kg/day.

The chronic dietary point of departure for the general population was based on the chronic toxicity study in dogs, where the LOAEL was 20 mg/kg/day (based on adverse liver findings (increased liver weights, increased centrilobular hepatocyte lipid in the liver, and increases in alkaline phosphatase, albumin, and triglycerides), increased adrenal cortical vacuolation of the zona fasciculata, and marked hemosiderin pigmentation in the liver and spleen in both sexes; mild anemia (characterized by decreased hemoglobin, hematocrit, and red blood cell count) in the males; and initial body weight losses, decreased cumulative body-weight gains, and increased adrenal weights in the females) and the NOAEL was 5 mg/kg/day. An UF of 100X (10-fold for interspecies extrapolation and 10-fold for intraspecies variability) was applied to the NOAEL of

5 mg/kg/day to derive the chronic reference dose (cRfD). The FQPA SF of 1X is applicable for chronic dietary risk assessment. Therefore, the chronic population-adjusted dose (cPAD) for the general population is 0.05 mg/kg/day.

Points of departure for short- and intermediate-term dermal and inhalation risk assessments were based on the prenatal developmental toxicity study in rabbits, where the LOAEL was 15 mg/kg/day and the NOAEL was 7.5 mg/kg/day. Points of departure for long-term dermal and inhalation risk assessments were not selected since exposures of these durations are not expected based on the use pattern. Since oral studies were selected for the dermal exposure assessment, a dermal-absorption factor of 21% (based on an *in vivo* rat dermal-absorption study) was used. Inhalation toxicity is assumed to be equivalent to oral toxicity. HED's level of concern (LOC) for flutriafol occupational and residential dermal and inhalation exposures is 100 (i.e., a margin of exposure (MOE) greater than 100 is not of concern to HED). The LOC is based on a 10X UF to account for inter-species extrapolation to humans from the animal test species and 10X UF to account for intra-species sensitivity.

Environmental Fate and Drinking Water Assessment
Flutriafol is a triazole fungicide and 1,2,4-triazole (T), which forms as a minor degradate of flutriafol, is a common degradate of conazole pesticides. T is not included in this assessment, but has been addressed in a separate assessment (EFED memo; D320682, I. Maher, 28-Feb-2006). The drinking water assessment for the parent is a Tier I, screening-level drinking water assessment using the Screening Concentration in Ground Water (SCI-GROW) and FQPA Index Reservoir Screening Tool (FIRST) models with the maximum application rate for apples. Flutriafol is expected to be persistent and moderately mobile in the environment, with its major routes of dissipation through biotic degradation in aquatic environmental compartments. Flutriafol is expected to degrade with a half-life of more than one year in terrestrial biotic environments. This persistence indicates that flutriafol does have the potential to build up in the soil as a result of application over multiple consecutive years. Maximum aquatic concentrations expected from the proposed new uses are acute exposure of 48.8 ppb in surface water, chronic exposure of 5.7 ppb in surface water, and 4.8 ppb for both acute and chronic exposure to groundwater. The surface water estimates were used in the dietary risk analysis.

Dietary Risk
Conservative acute and chronic aggregate (food + water) dietary risk assessments to support the Section 3 registration of flutriafol on apples and soybean were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, version 2.03) model, and assumed tolerance-level residues, 100% crop treated (CT), and DEEM™ version 7.81 default processing factors. Drinking water was included in the dietary assessments.

The acute (food + water) exposure risk estimate for females 13-49 years old was 3.7% aPAD at the 95th percentile of the exposure distribution, and is not of concern to HED. The acute (food + water) exposure estimates were <100% aPAD for the U.S. general population (<1.0% aPAD) and all population sub-groups; the most highly exposed population subgroup was infants (<1 year old) with <1.0% aPAD. Therefore, acute dietary exposure to flutriafol is not of concern to HED.

The chronic (food + water) exposure estimates were <100% cPAD for the U.S. general population (1.0% cPAD) and all population sub-groups; the most highly exposed population

subgroup was children 1-2 years old with 4.6% cPAD. Therefore, chronic dietary exposure to flutriafol is not of concern to HED.

HED has determined that T, triazole alanine (TA) and triazole acetic acid (TAA) are also potential residues of concern in plants and livestock for all triazole fungicides. However, these triazole-related residues will not be regulated for specific triazole pesticides, but will be evaluated for the entire class of triazole compounds. HED has recently completed a dietary risk assessment considering exposure to T and TA +TAA based on established and proposed uses of triazole fungicides (D350664, M. Doherty, 06-Oct-2008; did not include the flutriafol uses). The resulting acute and chronic exposure to T and TA/TAA were less than HED's level of concern (T: ≤36% aPAD and ≤54% cPAD; TA/TAA: 34% aPAD and ≤40% cPAD). HED concludes that revised T and TA/TAA dietary risk assessments are unnecessary for the following reasons: **(1)** incorporation of the flutriafol uses resulted in negligible changes to the T and TA/TAA residue estimates incorporated into the previous dietary analyses and **(2)** the T and TA/TAA drinking water estimates incorporated into the previous dietary analyses assumed an annual fungicide application rate of 10.38 lb ai/acre for nonagricultural uses and 2.0 lb ai/acre for agricultural uses and the formation of T and/or TA/TAA at 30.7% of the applied rate (EFED memo; D320682, I. Maher, 28-Feb-2006). Since the annual application rate for flutriafol is ≤0.63 lb ai/acre and since all environmental degradates were identified at <10% total radioactive residue (TRR), a revised drinking water assessment is unnecessary.

Residential Risk
As there are no registered or proposed uses of flutriafol that would result in residential exposure, a residential exposure assessment was not conducted.

Aggregate Risk
Acute and chronic aggregate risks are assessed based on dietary exposure from food and drinking water sources and are the same as reported for acute and chronic dietary exposure. Therefore, acute and chronic aggregate risks to flutriafol are not of concern to HED. As there are no registered or proposed uses of flutriafol that would result in residential exposure, short- and intermediate-term aggregate risks were not assessed.

Occupational Handler Risk
Based on the proposed uses on soybeans and apples, handlers may be potentially exposed to flutriafol. Handlers include mixer/loaders who handle concentrated liquid flutriafol and applicators using aerial or groundboom equipment, and flaggers for aerial applications. Short- and intermediate-term dermal and inhalation risks were assessed with a baseline layer of clothing, and with additional personal-protective equipment (PPE). Chemical-specific data were not available; therefore, surrogate data from the Pesticide Handlers Exposure Database (PHED) were used. The combined dermal and inhalation exposure risks for mixer/loaders are not of concern [i.e., MOEs>100], **provided the mixer/loaders wear protective gloves as directed on the label.** For aerial applicators, risks were assessed using engineering controls (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); pilots are not required to wear protective gloves. With this level of protection, there are no risks of concern for aerial applicators. With baseline attire, there are also no risks of concern for groundboom applicators and for flaggers.

Occupational Post-application Risk
Following flutriafol application to soybean and apples, occupational post-application exposure is

possible. Post-application activities may include scouting, maneuvering irrigation equipment, hand weeding, and hand harvesting. Risks are not of concern (i.e., MOE>100) on day 0 (restricted-entry interval (REI) = 12 hours) for all of the exposure activities. Based on the acute toxicity of flutriafol, the REI should be set at 24 hours (i.e., Category II for acute dermal).

Environmental Justice Considerations
Potential areas of environmental justice concerns, to the extent possible, were considered in this human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under Continuing Surveys of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. The database listed below has been determined to require a review of its ethical conduct. It has received the appropriate review. It was concluded it does not violate current ethical standards.

Studies reviewed for ethical conduct: The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

Regulatory Recommendations
Provided Revised Sections B and F are submitted and the petitioner submits flutriafol *per se* analytical standards to the Analytical Chemistry Laboratory (ACL), HED concludes that the toxicological, residue chemistry, and occupational/residential databases are sufficient to support a conditional registration for application of flutriafol to apple and soybean.

Tolerances are established for residues of flutriafol, including its metabolites and degradates, in or on the commodities listed below. Compliance with the following tolerance levels is to be determined by measuring only flutriafol [(±)-α-(2-fluorophenyl)-α-(4-fluorophenyl)-1*H*-1,2,4-triazole-1-ethanol]: apple - 0.20 ppm, soybean, seed - 0.35 ppm; grain, aspirated fractions - 2.2

ppm; cattle, liver - 0.02 ppm; goat, liver - 0.02 ppm; hog, liver - 0.02 ppm; horse, liver - 0.02 ppm; and sheep, liver - 0.02 ppm.

Data Gaps

Toxicology:

- As part of the new 40 CFR revised Part 158 requirement, an immunotoxicity study is required.

Chemistry:

- Information concerning the storage conditions/interval for the samples collected from the ruminant metabolism study; if the storage intervals were >6 months, then data demonstrating the stability of the metabolic profile in the various matrices will be required.
- Submission of storage stability data demonstrating the stability of T, TA, and TAA in the soybean matrices for the employed intervals (soybean seed - 16 months; soybean meal, hull, and oil - 12 months).
- Storage stability data for flutriafol, T, TA, and TAA in ruminant liver (139 days).

Occupational and Residential Exposure

- Change the REI on the proposed label from 12 hours to 24 hours.

2.0 Ingredient Profile

Flutriafol is a contact and systemic Group 3 triazole fungicide which acts primarily as an inhibitor of ergosterol biosynthesis, thereby interfering with synthesis of fungal cell membranes. In the U.S., there is currently only a soybean Section 18 Emergency Exemption and a corresponding time-limited soybean tolerance (set to expire December 2010) for residues of flutriafol *per se* at 0.10 ppm (40 CFR 180.629; 2 x 0.057 lb ai/acre; RTI = 18-20 days; PHI = 21 days). Flutriafol is sold in about 40 countries for use on such crops as grapes, stone fruit, pome fruit, cereals, oilseed rape, table and sugar beets, bananas, and soybeans.

Aside from a Section 18 Emergency Exemption for use on soybeans, there are currently no food/feed uses for flutriafol in the U.S.

2.1 Summary of Proposed Uses

The petitioner submitted a text description of the proposed apple and soybean application scenarios in Section B, as well as a draft label for a 1.04 lb ai/gal suspension-concentrate (SC) formulation (Topguard™ Fungicide, EPA File Symbol No. 67760-###; 12-hour REI; equivalent to a flowable-concentrate (FlC)). The label recommends application of flutriafol to apple for control of scab (*Venturia inaequalis*) and powdery mildew (*Podosphaera leucotricha*) and to soybean for control of rust (*Phakospora pachyrizi*), Frogeye Leaf Spot (*Cercospora sojina*), Cercospora Blight and Leaf Spot (*Cercospora kikuchii*), Brown Spot (*Septoria glycines*), and Powdery Mildew (*Microsphaera diffusa*). For apple scab resistance management, the label recommends that flutriafol be tank-mixed with a protectant fungicide and notes that soybean spray solutions may be tank mixed with other approved fungicides, herbicides, or insecticides (no tank mix partners are specified). The label does not include any rotational crop restrictions

and prohibits application through irrigation equipment.

The submitted use directions are sufficient to allow evaluation of the residue data relative to the proposed use. The petitioner should resolve the discrepancy between the use pattern listed for soybeans in Section B (proposed maximum seasonal rate is stated to be 0.18 lb ai/acre in the text and 0.21 lb ai/acre in the table) and the use pattern listed on the draft label (proposed maximum seasonal rate of 0.23 lb ai/acre); the submitted soybean field trial data will support a maximum seasonal rate of 0.23 lb ai/acre. A revised Section B with the following changes is requested: **(1)** the proposed minimum apple RTI of 7 days for apples is not supported by the crop field trial data; the use directions should be revised to specify a minimum apple RTI of 14 days; **(2)** the apple use directions should be amended to specify a minimum spray volume of >20 GPA (gallons per acre); **(3)** since the soybean and apple field trials did not include an adjuvant, the label should be revised prohibiting the addition of adjuvants to the spray solutions; **(4)** the soybean use directions should be limited to the application to soybeans harvested for the dried seed; and **(5)** the label should indicate that only soybean may be rotated to a treated field. **A revised Section B should be submitted.**

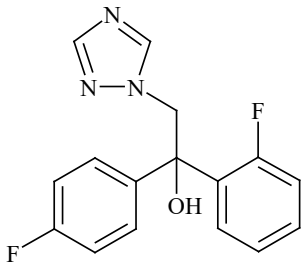
Table 2.1 summarizes the proposed use pattern and formulation specified in the end-use product containing flutriafol.

Table 2.1. Summary of Directions for Use of Flutriafol.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Apple						
Foliar, Broadcast, Equipment not specified	1.04 lb/gal FlC [67760-###]	0.07-0.11	6	0.63	14	Applications are to be initiated at green tip or when environmental conditions are favorable for primary scab development. RTI = 7-14 days.
Soybean						
Foliar, Broadcast, Ground or aerial	1.04 lb/gal FlC [67760-###]	0.06-0.11	3	0.23	21	Applications are to be made at the R3 growth stage or when conditions are favorable for disease development. RTI = 14-35 days. Only one application per growing season may be made at 0.11 lb ai/acre. Applications may be made using ground (≥10 gal/acre) or aerial (≥5 gal/acre) equipment. Feeding/grazing soybean forage/hay is prohibited.

2.2 Structure and Nomenclature

Table 2.2. Flutriafol Nomenclature.

Chemical structure	
Common name	Flutriafol
Company experimental name	PP450 (ICI/Syngenta until 2001)
IUPAC name	(*RS*)-2,4'-difluoro-α-(1*H*-1,2,4-triazol-1-ylmethyl)benzhydryl alcohol
CAS name	(±)-α-(2-fluorophenyl)-α-(4-fluorophenyl)-1*H*-1,2,4-triazole-1-ethanol
CAS registry number	76674-21-0
End-use product (EP)	1.04 lb ai/gal FlC formulation (Topguard™ Fungicide, EPA File Symbol No. 67760-XXX)

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Flutriafol.

Melting point/range	--	Not available
pH	6.1 in a 1% aqueous dilution	CSF for Flutriafol Technical dated 3/23/07
Density	0.99 g/cm3	
Water solubility	95 mg/L at 20 ºC	PP#7F7197 administrative materials
Solvent solubility	At 21 ºC g/L 1,2-Dichloroethane 19-20 Acetone 116-135 Ethyl acetate 29-34 Methanol 115-134 n-Heptane <10 Xylene <10	
Vapor pressure	4 x 10-7 Pa at 20 ºC	
Dissociation constant, pKa	2.3 at 25 ºC	
Octanol/water partition coefficient, Log(KOW)	log POW = 2.3 at 20 ºC	
UV/visible absorption spectrum	--	Not available

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Studies Available and Considered (Animal, Human, General Literature)

Acute toxicity – one each of oral, dermal, eye irritation, dermal irritation, skin sensitization studies on the technical (80% a.i.)
Subchronic toxicity – one 28-day dermal toxicity in rat, one oral 90-day rat, one oral 90-day dog
Chronic toxicity - one chronic oral dog, one chronic toxicity/carcinogenicity rat, one carcinogenicity mouse

Reproductive/developmental toxicity – two oral developmental rat, one oral developmental rabbit, one rat fertility/reproduction
Neurotoxicity – one acute neurotoxicity rat, one subchronic neurotoxicity rat
Mutagenicity- *in vitro* bacterial gene mutation, *in vitro* mouse lymphoma gene mutation, *in vitro* mammalian cytogenetics (chromosomal aberration assay human lymphocytes), *in vitro* mammalian cytogenetics (chromosomal aberration assay in rat bone marrow), erythrocyte micronucleus assay in mice, dominant lethal study, unscheduled DNA synthesis (UDS)

3.1.1.2 Mode of Pesticidal Action

Flutriafol is a member of the conazole triazole class of pesticides. The triazole fungicides inhibit one specific enzyme, C14-demethylase, which plays a role in sterol production. Sterols, such as ergosterol, are needed for fungal membrane structure and function, making them essential for the development of functional cell walls.

3.1.1.3 Sufficiency of Studies/Data

The toxicity database is complete for flutriafol for risk assessment evaluations and determination of the FQPA SFs. The acute dermal study was unacceptable; however, since there is an acceptable 28-day dermal study with no systemic effects seen up to the limit dose, there is no acute concern. Therefore, a new acute dermal study is not needed.

Note that while the new 40 CFR revised Part 158 requirement for an immunotoxicity study has not yet been fulfilled, the existing data are sufficient for endpoint selection for exposure/risk assessment scenarios and for evaluation of the requirements under FQPA.

3.1.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Flutriafol is quickly absorbed, extensively metabolized, and quickly eliminated (within 48 hours) regardless of sex, dose, or whether exposure was to single or multiple dosing regimens. More than 78% of the dose was recovered in the bile and urine. In the blood, radioactivity partitioned into the red blood cells. In both sexes and all groups, concentrations of radioactivity were relatively high in whole blood, liver, and kidneys. Other organs with high concentrations included the adrenal glands, spleen, and pituitary. The total amount of radioactivity isolated in the tissues and carcass was <1-3%. Bioaccumulation was considered unlikely. The parent was isolated in only trace amounts in the urine and feces and more than 19 metabolites were isolated, indicating extensive metabolism. The primary site for metabolism was the 2-fluorophenyl ring. The initial metabolic step was epoxidation followed by rearrangement to form either the dihydrodiol isomers or the hydroxy or dihydroxy metabolites. The hydroxyl groups on these primary metabolites may then be either conjugated with glucuronic acid or methylated. A second, minor route for metabolism of flutriafol was via the removal of the triazole ring to form 1-(2 fluorophenyl)-1-(4-fluorophenyl)-ethandiol, which is then conjugated with glucuronic acid.

3.1.3 Hazard and Dose-Response Characterization

Flutriafol appears to be generally equally toxic to rats, mice, and dogs with all three species having similar (within one order of magnitude) NOAELs/LOAELs. The target organ is the liver in dogs, rats, and mice. Hepatotoxicity occurred at similar dose levels across several species and

durations of exposure. Flutriafol has low acute toxicity via the oral and inhalation routes (Toxicity Category III and IV, respectively) in rats. There is no acceptable acute dermal toxicity study in the database. However, a 28-day dermal-toxicity study did not reveal any signs of toxicity at the limit dose (1000 mg/kg/day). Thus, flutriafol is not considered to be acutely toxic via the dermal route. Flutriafol is minimally irritating to the eyes (Toxicity Category III) and is not a dermal irritant (Toxicity Category IV). Flutriafol was not shown to be a skin sensitizer when tested in guinea pigs (Buehler method).

The pattern of toxicity attributed to flutriafol exposure via the oral route includes hepatotoxicity, developmental toxicity (manifested as increased intrauterine death) and generalized toxicity (body weight/body-weight gains and food consumption decrements as well as slight anemia).

Short-term, subchronic, and chronic toxicity studies in rats, mice, and dogs identified the liver as the primary target organ of flutriafol. Hepatotoxicity was first evident in the subchronic studies (rats and dogs) in the form of increases in liver enzymes (alkaline phosphatase), liver weights, and histopathology findings ranging from hepatocyte vacuolation to centrilobular hypertrophy and slight increases in hemosiderin-laden Kupffer cells. It is noteworthy that with chronic exposures, there are no indications of progression of liver toxicity in either species. After over one year of exposure, hepatotoxicity in rats, dogs, and mice took the form of (1) minimal to severe fatty change; (2) bile duct proliferation/cholangiolarfibrosis; (3) hemosiderin accumulation in Kupffer cells; (4) centrilobular hypertrophy, and (5) increases in alkaline phosphatase. Neither the chronic/carcinogenicity study in rats or the carcinogenicity study in mice revealed treatment-related increases in tumor incidences.

Slight indications of effects in the hematopoietic system are sporadically seen in the database. These effects are manifested in the form of slight anemia (rats and dogs) and increased platelet, white blood cell, neutrophil, and lymphocyte counts (mice). These effects, however, were minimal in severity.

3.1.4 Developmental and Reproductive Toxicity

The potential impact of *in utero* and perinatal flutriafol exposure was investigated in three developmental toxicity studies (two in rats, one in rabbits) and a multigeneration reproduction toxicity study in rats. Only one of the rat developmental toxicity studies was acceptable. In the acceptable rat developmental study, a qualitative susceptibility was noted. Although developmental toxicity occurred at the same dose level that elicited maternal toxicity, the developmental effects (external, visceral, and skeletal malformations; embryo lethality, skeletal variations, a generalized delay in fetal development and fewer live fetuses) were more severe than the decreased food consumption and body-weight gains observed in the dams. For rabbits, intrauterine deaths occurred at a dose level that also caused adverse effects in maternal animals. In the two-generation reproduction study, a qualitative susceptibility was seen. Effects in the offspring (decreased litter size and percentage of live births and liver toxicity) can be attributed to the systemic toxicity of the parental animals (decreased body weight and food consumption and liver toxicity).

3.1.5 Evidence of Neurotoxicity

Effects that may be considered signs of neurotoxicity (decreased motor activity and hindlimb grip strength, ptosis, lost righting reflex, hunched posture, ataxia) were reported in the acute and

subchronic neurotoxicity studies at the highest dose only. These effects, however, were primarily seen in animals that were agonal (at the point of death) and, thus are not indicative of neurotoxicity. This conclusion is further reinforced by the observation that there was no evidence of neurotoxicity in any additional short-term studies in rats, mice, and dogs, or in the long-term toxicity studies in rats, mice, and dogs. It is important to note that in the acute neurotoxicity study, for animals that did not die in the study or were sacrificed *in extremis,* all effects resolved by Day 8.

3.1.6 Immunotoxicity

There was no evidence of toxicity to the immune organs at the LOAEL in any study in the database. In addition, flutriafol does not belong to a class of chemicals (e.g., the organotins, heavy metals, or halogenated aromatic hydrocarbons) that would be expected to be immunotoxic. Based on the above considerations, HED does not believe that conducting a special series 870.7800 immunotoxicity study will result in a point of departure less than the cRfD NOAEL of 5 mg/kg/day for flutriafol; therefore, an additional UF for database uncertainties (UF_{DB}) does not need to be applied. Note that while the new 40 CFR revised Part 158 requirement for an immunotoxicity study has not yet been fulfilled, the existing data are sufficient for endpoint selection for exposure/risk assessment scenarios and for evaluation of the requirements under FQPA. Further, the data requirements pertaining to immunotoxicity (see Section 10.1) should be fulfilled as a condition of registration.

3.1.7 Additional Information from Literature Sources

A literature search, conducted on TOXLINE, did not reveal any other additional relevant information beyond what was included in the studies that were submitted by the registrant.

3.2 Dose-Response

The critical effects for flutriafol exposure via the oral route are hepatotoxicity, developmental toxicity (manifested as increased intrauterine death) in the presence of maternal toxicity, and generalized toxicity (body weight/body-weight gains and food consumption decrements as well as slight anemia). Hepatotoxicity, the primary toxic effect for this compound, was seen in all species tested with the first indications occurring after subchronic exposure, with LOAELs for this toxicity ranging from 15-20 mg/kg/day in dogs (subchronic and chronic exposures, respectively) to 200 mg/kg/day in rats. In general, duration of exposure does not seem to exacerbate toxicity as evidenced by the fact that the NOAELs/LOAELs for subchronic and chronic exposure are very similar and the nature and severity of effects does not appear to worsen with time.

3.3 Hazard Identification and Toxicity Endpoint Selection

A summary of the toxicological endpoints and doses chosen for the relevant exposure scenarios for human risk assessment is found in Table 3.8. See text below for rationales.

3.3.1 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: Prenatal Developmental Toxicity Study - Rabbit 870.3700b

Dose/Endpoint for Establishing the aRfD: The aRfD for females, age 13-49, was established based on the LOAEL from the developmental toxicity study in rabbits. The LOAEL of 15 mg/kg is based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss. The NOAEL was 7.5 mg/kg.

$$\text{aRfD} = \frac{\text{7.5 mg/kg (NOAEL)}}{\text{100 (UF)}} = \text{0.075 mg/kg}$$

Comments: The NOAEL selected provides the lowest NOAEL from any toxicity study in the flutriafol database in which a toxic response could be the outcome of 1-2 days of dosing. UFs for inter-species extrapolation (10X) and intra-species variation (10X) were retained for a total UF of 100.

3.3.2 Acute Reference Dose (aRfD) - General Population

Study Selected: Acute Neurotoxicity Study 870.6200a

Dose/Endpoint for Establishing the aRfD: The aRfD for the general population was established based on the LOAEL from the acute neurotoxicity screening battery in the rat. The LOAEL of 750 mg/kg is based on decreased body weight, body-weight gain, absolute and relative food consumption, agonal effects in both sexes (dehydration, urine-stained abdominal fur, ungroomed coat, ptosis, decreased motor activity, prostration, limp muscle tone, muscle flaccidity, hypothermia, hunched posture, impaired or lost righting reflex, scant feces), in males (red or tan perioral substance, chromodacryorrhea, chromorhinorrhea, labored breathing, and slight ataxia), and in females (piloerection and bradypnea). The NOAEL is 250 mg/kg.

$$\text{aRfD} = \frac{\text{250 mg/kg/ (NOAEL)}}{\text{100 (UF)}} = \text{2.5 mg/kg}$$

Comments: The NOAEL selected provides the lowest NOAEL from any toxicity study in the flutriafol database in which a toxic response occurred after a single exposure. Though these effects are not considered to be indicative of effects in the nervous system *per se* (they were considered agonal since they were primarily observed in animals that were moribund), they are nonetheless toxic effects and are, therefore, appropriate for risk assessment purposes. UFs for inter-species extrapolation (10X) and intra-species variation (10X) were retained for a total UF of 100.

3.3.3 Chronic Reference Dose (cRfD) – General Population

Study Selected: Chronic Toxicity Study - Dog 870.4200

Dose/Endpoint for Establishing the cRfD: The cRfD for the general population was established based on the NOAEL derived from the chronic oral toxicity study in dogs. The LOAEL of 20 mg/kg/day is based on adverse liver findings (increased liver weights, increased centrilobular hepatocyte lipid in the liver, and increases in alkaline phosphatase, albumin, and triglycerides), increased adrenal cortical vacuolation of the zona fasciculata, and marked hemosiderin pigmentation in the liver and spleen in both sexes, mild anemia (characterized by decreased hemoglobin, hematocrit, and red blood cell count) in the males, and initial body-weight losses, decreased cumulative body-weight gains, and increased adrenal weights in the females. The NOAEL is 5 mg/kg/day.

$$cRfD = \frac{5 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.05 \text{ mg/kg/day}$$

Comments: This NOAEL is lower than any NOAEL in the database for chronic effects. In addition, the study duration is appropriate for the duration of exposure. Both the 28-day dog and 90-day dog oral toxicity studies provide NOAEL/LOAELs and toxic effects of the same kind (adverse liver effects) and orders of magnitude as the chronic dog study. UFs for inter-species extrapolation (10X) and intra-species variation (10X) were retained for a total UF of 100.

3.3.4 Dermal Absorption

An *in vivo* rat dermal-absorption study is available for flutriafol that is acceptable and indicates that the absorption is 17%, 21%, and 11%, respectively, at 2, 20, and 200 $\mu g/cm^2$, following a 10-hour exposure. A value of 21% is appropriate (most protective) for dermal risk assessments.

3.3.5 Dermal Exposure (Short-, Intermediate-Term)

Study Selected: Prenatal Developmental Toxicity Study - Rabbit 870.3700b

Dose/Endpoint for Risk Assessment: The effects of concern that are relevant to the selection of the short- and intermediate-term dermal exposure are based on the LOAEL from the developmental toxicity study in rabbits. The LOAEL of 15 mg/kg is based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss. The NOAEL was 7.5 mg/kg.

Comments: The developmental toxicity study in rabbits is considered appropriate for this risk assessment. No effects were reported in the 28-day dermal toxicity study in rats at doses up to 1000 mg/kg/day (limit dose); however, that study did not evaluate the potential impact of flutriafol exposure on the developing organism or in pregnant females. A relatively steep dose-response was observed in the rabbit developmental study with a developmental NOAEL of 7.5 mg/kg/day and a developmental LOAEL of 15 mg/kg/day, based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss. Although maternal toxicity was also observed at 15 mg/kg/day, the effects were restricted to moderate decreases in bodyweight and food consumption, and were less severe than the effects observed in the offspring at the developmental LOAEL (15 mg/kg/day). In addition, although decreased body weight was an adverse effect observed in non-pregnant animals with flutriafol, results of this study indicate that pregnant animals were more sensitive to this effect.

Using a dermal-absorption factor of 21%, the dermal-equivalent dose is ~35.7 mg/kg/day (NOAEL of 7.5 mg/kg/day / 21% dermal absorption = 35.7 mg/kg/day).

3.3.6 Inhalation Exposure (Short- and Intermediate-Term)

Study Selected: Prenatal Developmental Toxicity Study - Rabbit 870.3700b

Dose/Endpoint for Risk Assessment: The effects of concern that are relevant to the selection of the short- and intermediate-term inhalation exposure are based on the LOAEL from the developmental toxicity study in rabbits. The LOAEL of 15 mg/kg is based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss. The NOAEL was 7.5 mg/kg.

Comments: With the exception of an acute inhalation toxicity study (intended to establish the

LC_{50}), there are no inhalation toxicity studies in the flutriafol database. Developmental toxicity was observed in the rabbit oral developmental study. The developmental rabbit study had a developmental NOAEL of 7.5 mg/kg/day and a developmental LOAEL of 15 mg/kg/day, based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss.

Inhalation toxicity is assumed to be equivalent to oral toxicity.

3.3.7 Long-term (>6 Months) Dermal and Inhalation

Based on the use pattern, long-term dermal and inhalation exposure for workers and homeowners is not expected to occur; therefore, a long-term risk assessment is not required.

3.3.8 Level of Concern for Margin of Exposure

Table 3.3.9. Summary of LOC for Risk Assessment[1].

Route	Short-Term MOE (1-30 Days)	Intermediate-Term MOE (1-6 Months)	Long-Term MOE (>6 Months)[2]
Occupational (Worker) Exposure[1]			
Dermal	<100	<100	-
Inhalation	<100	<100	-
Residential Exposure[1]			
Dermal	100	<100	-
Inhalation	<100	<100	-

[1] LOC based on UF_A = 10X [(extrapolation from animal to human (intra-species); UF_H = 10X [potential variation in sensitivity among members of the human population (inter-species)]. FQPA SF = 1X.

[2] Long-term exposures are not expected for the exposure scenarios listed.

3.4 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, an aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. As there are no registered or proposed uses of flutriafol that would result in residential exposure, short- and intermediate-term aggregate risks were not assessed.

3.5 Determination of Susceptibility

There is some evidence of increased qualitative, but not quantitative, susceptibility following *in utero* exposure to flutriafol. In an acceptable/guideline rabbit developmental toxicity study, developmental effects were observed at a dose level that also induced maternal toxicity. In an acceptable/guideline rat developmental toxicity study, flutriafol exposure resulted in decreased body weight and food consumption in dams and increased late resorptions, malformations and variations in several bones in offspring at the same dose. In the two-generation reproduction study in rats, offspring toxicity occurred at the same dose level at which parental toxicity occurred for the parameters measured.

3.5.1 Degree-of-Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

There is no evidence for quantitative susceptibility following *in utero* exposures to rats or rabbits and following pre-and post-natal exposures to rats for two generations. There is evidence for increased qualitative susceptibility in a prenatal study in rats and rabbits and the two generation reproductions study in rats, however, there is no concern for these observations since: 1) the effects were seen in the presence of maternal/parental/systemic toxicity; 2) clear NOAELs and LOAELs were established in the fetuses/offspring; 3) the dose-response for these effects are well defined and characterized; and 4) developmental endpoints are used for assessing acute dietary risks to the most sensitive population (females 13-49) as well as all other short- and intermediate-term exposure scenarios. Additionally, there are no residential uses and thus no potential exposure for infants and children.

3.5.2 Recommendation for a DNT Study

A DNT study is not required. This decision is based on the following observations:

- The clinical signs reported in the acute and subchronic neurotoxicity studies are not considered to be indicative of neurotoxicity, but rather were determined to be agonal (i.e., at the point of death).
- There are no indications of structural or functional neurological deficits in any of the other studies in the database.

3.6 FQPA Considerations

The flutriafol risk assessment team recommends that the 10X FQPA SF be reduced to 1X. This recommendation is based on the following considerations:

- Except for an immunotoxicity study, the toxicological database is complete.
- In accordance with the revised Part 158 an immunotoxicity study in required. In the case of flutriafol there was no evidence of toxicity to the immune organs in any study in the database. In addition, flutriafol does not belong to a class of chemicals (e.g., the organotins, heavy metals, or halogenated aromatic hydrocarbons) that would be expected to be immunotoxic. Based on the above considerations, HED does not believe that conducting a special series 870.7800 immunotoxicity study will result in a point of departure lower than that used for overall risk assessment. Therefore an additional UF_{DB} does not need to be applied.
- There are no concerns or residual uncertainties for pre- and/or post-natal toxicity. As noted above, although there is evidence for increased qualitative susceptibility in a prenatal study in rats and rabbits and the two generation reproductions study in rats, there is no concern for these observations since: 1) the effects were seen in the presence of maternal/parental/systemic toxicity; 2) clear NOAELs and LOAELs were established in the fetuses/offspring; 3) the dose-response for these effects are well defined and characterized; and 4) developmental endpoints are used for assessing acute dietary risks to the most sensitive population (females 13-49) as well as all other short- and intermediate-term exposure scenarios.
- There is no concern for neurotoxicity with flutriafol. Signs of neurotoxicity were reported in the acute and subchronic neurotoxicity studies at the highest dose only; however, these

effects were primarily seen in animals that were agonal (at the point of death) and, thus are not indicative of neurotoxicity. In addition, there was no evidence of neurotoxicity in any additional short-term studies in rats, mice, and dogs, or in the long-term toxicity studies in rats, mice, and dogs.

- A developmental neurotoxicity study is not required**.**
- The dietary exposure assessment is conservative in nature (utilize tolerance level residues and 100% CT).
- There are no proposed residential uses.

3.7 Classification of Carcinogenic Potential

Flutriafol is considered to be "Not likely to be Carcinogenic to Humans" based on the results of the carcinogenicity studies in rats and mice. The results of the rat chronic toxicity/carcinogenicity study and the mouse carcinogenicity study are negative for carcinogenicity. All genotoxicity studies on flutriafol showed no evidence of clastogenicity or mutagenicity. Although several triazoles are carcinogenic, many are not and flutriafol has been adequately tested and found not to be carcinogenic in long-term studies in rats and mice.

Structure-activity-relationship (SAR) analysis indicates that flutriafol may have the potential to produce thyroid and/or liver tumors in rodents. However, in the rat and mouse carcinogenicity studies, there were no treatment-related increases in tumor incidence when comparing treated animals to controls.

3.8 Summary of Toxicological Doses and Endpoints for Flutriafol for Use in Human Risk Assessments

A summary of the toxicological endpoints and doses chosen for the relevant exposure scenarios for human risk assessment are found in Table 3.8.

Table 3.8. Summary of Toxicological Doses and Endpoints for Flutriafol for Use in Dietary and Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA SFs	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females, 13-49 years of age)	NOAEL = 7.5 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 0.075 mg/kg/day aPAD = 0.075 mg/kg	Developmental study – rabbit LOAEL = 15 mg/kg, based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss.
Acute Dietary (General Population, Including Infants and Children)	NOAEL = 250 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 2.5 mg/kg/day aPAD = 2.5 mg/kg/day	Neurotoxicity screening battery – rat LOAEL = 750 mg/kg, based on decreased body weight, body-weight gain, absolute and relative food consumption, and clinical signs of toxicity in both sexes: dehydration, urine-stained abdominal fur, ungroomed coat, ptosis, decreased motor activity, prostration, limp muscle tone, muscle flaccidity, hypothermia, hunched posture, impaired or lost righting reflex, scant feces; in males: red or tan perioral substance, chromodacryorrhea, chromorhinorrhea and labored breathing, and in females: piloerection and bradypnea.

Table 3.8. Summary of Toxicological Doses and Endpoints for Flutriafol for Use in Dietary and Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA SFs	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All Populations)	NOAEL = 5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.05 mg/kg/day cPAD = 0.05 mg/kg/day	Chronic toxicity – dog LOAEL = 20 mg/kg/day, based on adverse liver findings (increased liver weights, increased centrilobular hepatocyte lipid in the liver, and increases in alkaline phosphatase, albumin, and triglycerides), increased adrenal cortical vacuolation of the zona fasciculata, and marked hemosiderin pigmentation in the liver and spleen in both sexes; mild anemia (characterized by decreased hemoglobin, hematocrit, and red blood cell count) in the males; and initial body weight losses, decreased cumulative body-weight gains, and increased adrenal weights in the females.
Dermal Short (1-30 days)- and Intermediate (1-6 months) -Term	NOAEL= 7.5 mg/kg/day Dermal-absorption factor = 21%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential/ Occupational LOC for MOE = 100	Developmental toxicity – rabbit LOAEL = 15mg/kg, based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss.
Dermal Long-Term (>6 months)	-	-	-	Based on the use pattern, long-term dermal and intermediate exposure for workers is not expected to occur, therefore, a long-term risk assessment is not required.
Inhalation Short (1-30 days)- and Intermediate (1-6 months) -Term	NOAEL = 7.5 mg/kg/day Inhalation toxicity assumed to be equivalent to oral toxicity	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential/ Occupational LOC for MOE = 100	Developmental toxicity – rabbit LOAEL = 15 mg/kg, based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss.
Inhalation Long-Term (>6 months)	-	-	-	Based on the use pattern, long-term dermal and intermediate exposure for workers is not expected to occur; therefore, a long-term risk assessment is not required.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the carcinogenicity studies in rats and mice.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

3.9 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) *"may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."* Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential

effects in wildlife. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, flutriafol may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

Literature searches were not performed by the registrant. A cursory review of human exposure to flutriafol on the internet yielded no additional information.

5.0 Dietary Exposure/Risk Characterization

References:
D355605, R. Daiss, 3-Sep-2008 (Residue of Concern Knowledge-Base Subcommittee (ROCKS) decision memorandum)
D360863, L. Shanaman, 1-Jan-2009 (flutriafol drinking water assessment)
D340513, T. Bloem, 11-Mar-2009 (flutriafol residue chemistry summary)
D355939, T. Bloem, 11-Mar-2009 (flutriafol dietary exposure analysis)
D359490, M. Doherty, 09-Dec-2008 (T, TA/TAA risk assessment)
D350664, M. Doherty, 06-Oct-2008 (T, TA/TAA dietary exposure analysis)
D320682, I. Maher, 28-Feb-2006 (T, TA/TAA drinking water assessment)

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The petitioner submitted adequate apple, sugar beet, and rapeseed metabolism studies conducted with [triazole-3,5-^{14}C]flutriafol and [carbinol-^{14}C]flutriafol (1 x 0.010-0.12 lb ai/acre). The radiolabel position did not affect TRRs or the metabolic profile for rapeseed (forage, pod, and mature seed; PHI = 0-21 days) or sugar beet tops (TRRs in root were too low for a comparison; PHI = 0-21 days); for apple (PHI = 64 days), TRRs were slightly higher following treatment with [triazole-3,5-^{14}C]flutriafol, but the resulting metabolic profiles did not vary with radiolabel position. Flutriafol (50-96% TRR) was the major residue identified in the apple, rapeseed (foliage, pod, and seed), and sugar beet tops (TRR in roots too low for identification). Defluorinated flutriafol (12-14% TRR) and conjugated flutriafol (27-28% TRR) were identified at significant concentrations in rapeseed pod. All other identified/unknowns were ≤8% TRR (T, TA, and TAA were not identified). Wheat and barley metabolism studies (foliar and seed treatment) were also submitted, but were deemed unacceptable due to numerous deficiencies.

5.1.2 Metabolism in Rotational Crops

The petitioner submitted a confined rotational crop study; however, this study was determined to be inadequate for the following reasons: **(1)** the study did not include a leafy vegetable crop; **(2)** residues in wheat forage were not investigated; **(3)** sandy loam soil was not used and no data were provided concerning the soil characteristics; **(4)** insufficient information was provided concerning analytical methodology and a confirmatory method was not used for the identification of metabolites; **(5)** insufficient information was provided to determine whether identification/characterization of residues met Agency requirements (e.g., five unknowns designated "others" accounted for up to >50% of TRR in carbinol-label sugar beet tops and were not further investigated; reference standards used were not identified); **(6)** insufficient attempts were made to characterize nonextractable residues of 120-day wheat straw and grain and 365-

day wheat straw samples; **(7)** insufficient storage stability data/information are available to support the storage interval of at least 4 years; and **(8)** insufficient information/data in general were provided to support the study, including details of sample handling at the field site and analytical laboratory; the distribution of radioactivity into sample extracts and fractions; representative chromatograms, raw data, or example calculations; and storage conditions and durations. Based on these deficiencies, HED does not believe the study is upgradeable and a new confined rotational crop study conducted with [triazole-3,5-^{14}C]flutriafol and [carbinol-^{14}C]flutriafol as specified in OPPTS 860.1850 should be submitted.

5.1.3 Metabolism in Livestock

Poultry: The petitioner submitted a hen metabolism study conducted with [triazole-3,5-^{14}C]flutriafol and [carbinol-^{14}C]flutriafol at a dietary rate of 13.9 ppm (160x) and 11.6 ppm (130x), respectively. TRRs were consistently higher following dosing with [triazole-3,5-^{14}C]flutriafol and significant differences were noted in the metabolic profiles depending on radiolabel position. Flutriafol was identified as a significant residue in [triazole-3,5-^{14}C]flutriafol and [carbinol-^{14}C]flutriafol samples (non-detect - 80% TRR). T (11-75% TRR) was identified as a significant residue in [triazole-3,5-^{14}C]flutriafol samples. An unknown, M3, was identified at significant concentrations following dosing with [carbinol-^{14}C]flutriafol (6-46% TRR); M3 was also identified at similar concentrations following dosing with [triazole-3,5-^{14}C]flutriafol, but at lower %TRR (3-11% TRR) due to the higher TRRs in these samples. All other identified/unknown residues were found at <10% TRR.

Ruminants: The petitioner submitted a dairy cow metabolism study conducted with [triazole-3,5-^{14}C]flutriafol at a dietary rate of 2 ppm (10x); a [carbinol-^{14}C]flutriafol study was not submitted. TRRs were ≤0.01 ppm in all commodities, excluding kidney (0.061 ppm) and liver (0.291 ppm). The major residues identified in kidney and liver were flutriafol (7-29% TRR) and M1B (4-hydroxy flutriafol; 1-23% TRR); TRRs in milk appeared to plateau by day 4. The following deficiencies were identified in the dairy cow metabolism study: **(1)** a confirmatory method was not used for the identification of metabolites; **(2)** no information concerning storage duration was provided; **(3)** reference standards for the triazole metabolites (T, TA, and TAA) were not included; and **(4)** the GLP statement indicated that since Cheminova (the petitioner) did not conduct the study and was not the sponsor, they could not be certain that the study was conducted in accordance with GLP practices (40 CFR 160). In addition, supporting information and data were extremely limited for this study.

5.1.4 Analytical Methodology

Residue Analytical Methods - Primary Crops: For tolerance enforcement, the petitioner is proposing the following methods: apple - the Food and Drug Administration (FDA) Multiresidue Method (MRM) Protocol D [Section 302 E1 (acetone extraction); analysis using module DG5)] and soybean - the GC/nitrogen/phosphorus detector (NPD) method employed in the field trials [acetonitrile (ACN):water extraction (70:30, v:v)]. As part of the MRM testing for flutriafol, the petitioner demonstrated that Protocol D [Section 302 E1 (acetone extraction); analysis using module DG5 (GC/NPD)] adequately recovered flutriafol residues from apples fortified at 0.1 ppm and 0.5 ppm (see FDA MRM section below). The proposed soybean enforcement method was validated in conjunction with the soybean magnitude of the residue studies and an adequate independent laboratory validation (ILV) was also submitted. The petitioner did not submit radiovalidation data for the proposed apple enforcement method; since

the extraction procedures for the proposed apple enforcement method are similar to those used in the apple metabolism study [ACN and ACN:water (1:1, v:v), and/or water; flutriafol identified only in the extracts], HED concludes that radiovalidation is unnecessary for apple. The petitioner did submit adequate radiovalidation for the proposed soybean method using rapeseed seed samples from the metabolism study. Therefore, HED concludes that the proposed soybean seed and apple tolerance enforcement methods are adequate and forwarded these methods to the FDA for inclusion in the Pesticide Analytical manual (PAM; D362421, T. Bloem, 11-Mar-2009).

Residue Analytical Method - Livestock: For enforcement of the ruminant liver tolerance, the petitioner is proposing method ICIA AM00306 (revisions of 13-Aug-2007 and 8-Oct-2007). This method was validated in conjunction with the ruminant feeding study and an adequate ILV was also submitted. The petitioner did not include radiovalidation data for this method. Based on the extraction solvent used for liver (ACN) and that used in the livestock metabolism studies [ACN:water (1:1 (v:v))] , radiovalidation data are unnecessary. Therefore, HED concludes that the proposed ruminant liver tolerance enforcement method is adequate and forwarded this method to the FDA for inclusion in PAM (D362421, T. Bloem, 11-Mar-2009).

FDA MRM: Based on the decision tree provided in Appendix II of the FDA PAM I, flutriafol was tested through Protocols A, C (modules DG1 and DG 5 only), D, E, and F. Protocols A, E, and F were determined to be unacceptable for determination of flutriafol due to unacceptable recoveries from the clean-up column and/or unacceptable analytical response using the specified conditions. Flutriafol yielded acceptable instrument response using the Protocol C gas-liquid chromatograph (GLC) conditions specified in modules DG1 [electron-capture detector (ECD)] and DG5 (NPD). Flutriafol yielded acceptable recoveries through protocol D (Section 302 E1; acetone extraction) using a non-fatty matrix (apple) fortified at 0.1 ppm [116% (n=2)] and 0.5 ppm (112% and 155%) and quantified using module DG5 (NPD); HED notes that matrix blanks were not analyzed. These data were forwarded to FDA (D355835, T. Bloem, 3-Sep-2008).

5.1.5 Environmental Degradation

Flutriafol is expected to be persistent and moderately mobile in the environment, with its major routes of dissipation through biotic degradation. Flutriafol is expected to degrade with a half-life of more than one year in the environment. Batch equilibrium data on flutriafol suggest that the compound will sorb to soil with moderate affinity, and display moderate mobility (Kd values range from 2.0 to 13.6). The compound does not volatilize significantly, with a partial vapor pressure of 4×10^{-7} Pa at 20 °C. Therefore, dissipation in the environment is expected to occur via runoff of dissolved residues, and sorption to eroding sediments. Flutriafol leachate is expected to persist in both aerobic and anaerobic soil compartments.

Flutriafol biodegrades with half-lives of more than a year in both aerobic and anaerobic terrestrial and aquatic environments, and is expected to persist for years in both aerobic and anaerobic environments. Additionally, flutriafol is stable to both hydrolysis and aquatic photolysis. Dissipation occurred with half-lives of 106 to 13,566 days in terrestrial field studies, which is consistent with the submitted, laboratory-derived data. Due to the length of the studies, and the persistence of flutriafol, major degradates were not detected in either laboratory or field studies. Minor degradates of flutriafol (which were only reported in two studies: a soil photolysis study and an anaerobic aquatic metabolism study) include: T, TAA, TA, 2,4'-difluorobenzophenone, and CO_2.

5.1.6 Comparative Metabolic Profile

In rat metabolism studies, parent was isolated in only trace amounts in the urine and feces (<0.5% of the administered dose) and more than 19 metabolites were isolated (<0.1-16% of the administered dose). In rats, the primary site for metabolism was the 2-fluorophenyl ring. The initial metabolic step was probably epoxidation followed by either rearrangement to form the dihydrodiol isomers or to form hydroxy or dihydroxy metabolites. The hydroxyl groups on these primary metabolites may then be either conjugated with glucuronic acid or methylated. A second, minor route for metabolism of flutriafol was via the removal of the triazole ring to form 1-(2 fluorophenyl)-1-(4-fluorophenyl)-ethandiol, which is then conjugated with glucuronic acid.

Flutriafol (free and conjugate) was the major residue identified in the apple, sugar beet, and rapeseed metabolism studies; defluorinated flutriafol was also identified in rapeseed. The ruminant metabolism study resulted in TRRs ≤0.01 ppm in all samples, except for liver and kidney. The major residues identified in liver and kidney were flutriafol and M1B (4-hydroxyflutriafol), with minor amounts of M1D (4-hydroxy-5-methoxyflutriafol) also identified. The poultry metabolism study yielded sufficient radioactivity in all matrices for residue identification, with flutriafol and T being the major identified residues. An unknown, M3, was identified at significant concentrations following dosing with [carbinol-^{14}C]flutriafol; M5 (hydroxylated flutriafols) was also identified, but at an insignificant concentration. The submitted confined rotational crop study has been determined to be unacceptable.

5.1.7 Toxicity Profile of Major Metabolites and Degradates

Based on structural similarity, HED concludes that the defluorinated and hydroxylated flutriafols identified in the plant and livestock metabolism studies are not likely to be more toxic than flutriafol. HED has previously reviewed toxicological data for T, TA, and TAA and concluded that the toxicological effects of T and TA/TAA are different from each other (D322215, M. Doherty *et al.*, 07-Feb-2006). Based on these data and the flutriafol toxicological data, HED concludes that the toxicological effects of T and TA/TAA are different from that of flutriafol.

5.1.8 Pesticide Metabolites and Degradates of Concern

The HED ROCKS met on 12-August-2008 to discuss the residues of concern in apple, dried soybean seed, and livestock (D355605, R. Daiss, 03-Sep-2008). Table 5.1.8.1 and the following paragraphs are summaries of the ROCKS conclusions (see Appendix D for chemical names and structures). Since flutriafol contains fluorine, HED evaluated the potential for increased exposure to fluoride as a result of the proposed application scenarios; based on the plant, livestock, and environmental metabolism/degradation studies, HED concludes that exposure to fluoride from flutriafol is negligible (see below).

Table 5.1.8.1 Summary of Metabolites and Degradates of Concern for Risk Assessment and Tolerance Enforcement.

Matrix	Residues of Concern	
	Risk Assessment[1]	Tolerance Enforcement
soybean seed	flutriafol, T, TA, and TAA	flutriafol
apple		
poultry[2]		
ruminant[3]	flutriafol, M1B, T, TA, and TAA	
water	flutriafol and T	not applicable

[1] The ROCKS concluded that based on the toxicity of the residues of concern, three risk assessments are necessary when evaluating the exposure resulting from application of flutriafol [flutriafol and M1B; T (1,2,4-triazole); and TA (triazolylalanine) and TAA (triazolylacetic acid)].

[2] HED notes that if the poultry dietary burdens increase, these conclusions will be revisited and poultry metabolism studies

conducted as specified in OPPTS 860.1300 with [carbinol-^{14}C]flutriafol and [triazole-3,5-^{14}C]flutriafol may be required.

[3] HED notes that if the ruminant dietary burden increases, these conclusions will be revisited and ruminant metabolism studies conducted as specified in OPPTS 860.1300 with [carbinol-^{14}C]flutriafol and [triazole-3,5-^{14}C]flutriafol may be required.

Apple and Dried Soybean Seed: Based on the apple, sugar beet and rapeseed metabolism data, the ROCKS concluded that the residues of concern in apple and dried soybean seed are flutriafol, T, TA, and TAA and the residue of concern for tolerance enforcement is flutriafol *per se*. Defluorinated flutriafol and conjugated flutriafol were not included as residues of concern since apple and dried soybean seed do not possess a commodity similar to rapeseed pod (label prohibits feeding/foraging soybean forage/hay and use will be restricted to only soybean harvested for the dried seed). For future uses on legumes other than dried seeds, defluorinated flutriafol and conjugated flutriafol should be included for risk assessment. T, TA, and TAA were included as residues of concern as they were identified in the apple and soybean field trial studies and/or to be consistent with the other triazole fungicides.

Poultry: Based on the poultry metabolism study, the ROCKS concluded that the residues of concern in poultry for risk assessment are flutriafol, T, TA, and TAA and the residue of concern for tolerance enforcement is flutriafol *per se*. Residues of TA and TAA were included as residues of concern due to their presence in feed commodities. M3 was excluded as a residue of concern since residues are expected to be negligible when normalized to the current dietary burden. **HED notes that if the poultry dietary burdens increases, these conclusions will be revisited and poultry metabolism studies conducted as specified in OPPTS 860.1300 with [carbinol-^{14}C]flutriafol and [triazole-3,5-^{14}C]flutriafol may be required.**

Ruminants: Based on the results of the dairy cow metabolism study and for the reasons listed below, the ROCKS concluded that the residues of concern for risk assessment in ruminants are flutriafol, M1B, T, TA, and TAA and the residue of concern for tolerance enforcement is flutriafol *per se*. The reasons include: **(1)** based on (a) the DEREK analysis, which did not result in alerts for potential flutriafol metabolites without the triazole ring; (b) the rat metabolism study, which resulted in the identification of a metabolite without the triazole ring in urine and feces (M18; <1-8% of the administered dose); and (c) the fact that developmental toxicity demonstrated for many of the triazole fungicides, including flutriafol, is likely a result of the triazole ring, HED concludes that flutriafol metabolites without the triazole ring are not likely to be more toxic than parent (a [carbinol-^{14}C]flutriafol ruminant metabolism study has not been submitted); **(2)** based on the TRRs from the [triazole-3,5-^{14}C]flutriafol dairy cow metabolism study (10x) and because the hen metabolism study resulted in higher TRRs following dosing with [triazole-3,5-^{14}C]flutriafol as compared to [carbinol-^{14}C]flutriafol, residues in all ruminant commodities, excluding liver and kidney, are expected to be insignificant [liver - 0.291 ppm; kidney - 0.061 ppm; all other tissues ≤0.01 ppm; and milk - ≤0.008 ppm (TRRs in milk appeared to plateau by day 4)]; and **(3)** the ruminant feeding studies resulted in low flutriafol *per se* residues when normalized to 1x the current maximum reasonable dietary burden (MRDB; liver ≤0.013 ppm; kidney ≤0.002 ppm; fat ≤0.002 ppm; muscle ≤0.0008 ppm; and milk <0.001 ppm). Residues of TA and TAA were included as residues of concern due to their presence in feed commodities. **HED notes that if the ruminant dietary burden increases, these conclusions will be revisited and ruminant metabolism studies conducted as specified in OPPTS 860.1300 with [carbinol-^{14}C]flutriafol and [triazole-3,5-^{14}C]flutriafol may be required.**

Water: Based on the environmental fate data, the ROCKS concluded that the residues of concern in water are flutriafol and T.

Fluoride: Defluorinated flutriafol was not identified in the apple, sugar beet, wheat, livestock, or environmental metabolism/degradation studies (acceptable confined rotational crop study has not been submitted). Defluorinated flutriafol was identified in the canola metabolism study [pod without the seed - 12-15% TRR (≤0.12 ppm); seed - 4% TRR (≤0.05 ppm)]. Using the canola metabolism data as a surrogate for soybean and accounting for application rate, a fluoride residue of 0.006 ppm in soybean seed resulting from application of flutriafol was calculated.

HED has previously conducted separate dietary exposure analyses for fluoride resides from the insecticides cryolite and sulfuryl fluoride as well as from naturally occurring fluoride residues in food and water. It was noted that many pesticides contain the fluorine atom, but it was assumed that only cryolite and sulfuryl fluoride would result in meaningful increases in fluoride residues as compared to background levels (presumably due to the lack of carbon-fluorine bonds in these two compounds). Table 5.1.8.2. is a summary of the fluoride residue estimate in soybean from flutriafol and the fluoride residue estimates incorporated into the sulfuryl fluoride and background dietary exposure analyses (cryolite not registered for use on soybean). Based on this comparison, flutriafol is not a significant contributor to fluoride residues in soybean.

Fluoride residues from flutriafol in apple, livestock, and water were considered negligible for the following reasons: apple - the apple metabolism study did not result in the identification of defluorinated flutriafol; livestock - fluoride concentrations in plant leaves usually range from 0.1 to 15 ppm (http://www.inchem.org/documents/ehc/ehc/ehc227.htm#5.1); concentrations which are several orders of magnitude greater than that estimated for soybean; and water - the environmental fate/degradation studies did not result in the identification of defluorinated flutriafol.

Table 5.1.8.2 Summary of Fluoride Residues in Soybean from Flutriafol, Sulfuryl Fluoride, and Background.

Source	Commodity	Fluoride Residue*	Comments
flutriafol	soybean seed	0.006 ppm	assumes 100% crop treated; based on the canola metabolism data and accounting for application rate
background	soybean seed, flour, milk, and oil	0.494 ppm	D309014; residues in bean cooked in fluoridated water
sulfuryl fluoride	soybean flour	0.081 ppm	D362183; residue from structural fumigation; percent treated estimates incorporated into the residue estimate
sulfuryl fluoride	soy milk	2.4 ppm (0.0096 ppm)	D362183; residue from structural fumigation; only 0.4% of soy milk is expected to be treated
sulfuryl fluoride	soy oil	1.5 ppm (0.006 ppm)	D362183; residue from structural fumigation; only 0.4% of soy oil is expected to be treated

* Residue in parenthesis accounts for percent crop treated.

5.1.9 Drinking Water Residue Profile

Hydrolysis and aqueous photolysis of flutriafol are very slow. In soil, flutriafol is persistent, with a biotic half-life value greater than one year. Flutriafol degrades more rapidly under aerobic aquatic environments, with a half-life value of approximately 6 weeks in an aerobic water/sediment test system. No major degradation products (i.e., >10% of applied) were

identified in any water or soil studies.

Flutriafol is moderately mobile in laboratory tested soils. This moderate potential for mobility, combined with the persistence demonstrated by laboratory metabolism half-lives greater than one year, indicate that under some environmental conditions, flutriafol does possess the potential to reach groundwater. Flutriafol residues have been detected in surface samples taken from the Svalbard archipelago ice cap in arctic Norway indicating a potential for long range transport. Six terrestrial field dissipation studies with applications made over several consecutive years, most with applications over multiple years, indicate that flutriafol residues will remain undegraded, allowing residues to carry-over from year to year under actual use conditions.

Due to the length of the studies, and the persistence of flutriafol, major degradates were not detected in either laboratory or field studies. Minor degradates of flutriafol, which were only reported in two studies, a soil photolysis study and an anaerobic aquatic metabolism study, include T, TAA, TA, 2,4'-difluorobenzophenone, and CO_2. With the exception of T, none of the degradates above were considered a residue of concern by the ROCKS. T was a minor degradate in the submitted studies, but is a common degradate to other fungicides. T is not included in this assessment, but has been addressed in a separate assessment (EFED memo; D320682, I. Maher, 28-Feb-2006).

The drinking water assessment is a Tier 1, screening-level drinking water assessment using the SCIGROW and FIRST models with the maximum application rate for apples. Maximum aquatic concentrations expected from the proposed new uses are an acute exposure of 48.8 ppb in surface water, a chronic exposure of 5.7 ppb in surface water, and 4.8 ppb for both acute and chronic exposure to ground water, all resulting from use of flutriafol at the proposed maximum labeled application rate to apples. Proposed maximum use rates for soybeans produced lower estimated drinking-water concentrations (EDWCs).

Table 5.1.9. Summary of EDWCs for Flutriafol.

	Flutriafol	
	Surface Water Conc., ppb[1]	Groundwater Conc., ppb[2]
Acute	48.8	4.8
Chronic (non-cancer)	5.7	4.8

[1] From the FIRST (Version 1.1, 12/12/05) model. Input parameters are based on 0.11 lbs a.i./acre per application with a 7-day minimum interval between applications and six applications per season (apples). The percent cropped area (PCA) factor was 0.87.

[2] From the SCI-GROW model assuming a maximum seasonal use rate of 0.11 lbs ai/A, a K_{oc} of 140 mL/g, and a half-life of 588 days.

5.1.10 Food Residue Profile

Magnitude of the Residue - Apple and Soybean Raw Agricultural Commodities (RACs):
Pending submission of supporting storage stability data for T, TA, and TAA in/on soybean seed, the submitted apple and soybean field trial data are acceptable. The number and locations of the field trials are in accordance with OPPTS Guideline 860.1500 requirements. The field trials employed the requested formulation and, provided the petitioner submits a revised Section B, the application scenarios were appropriate. The harvested samples were analyzed for residues of flutriafol, T, TA, and TAA using acceptable methods. Residues of flutriafol, T, TA, and/or TAA in/on apple were as follows: flutriafol - 0.029-0.138 ppm (controls <0.01 ppm), T - <0.01 ppm

(controls <0.01 ppm), TA - <0.01-0.052 ppm (controls <0.01-0.060 ppm), and TAA - <0.01 – 0.012 ppm (controls <0.01 ppm). Residues of flutriafol, T, TA, and/or TAA in/on dried soybean seed were as follows: flutriafol - <0.01-0.306 ppm (controls <0.01 ppm), T - <0.01 ppm (controls <0.01 ppm), TA - 0.038-0.670 ppm (controls 0.028-1.34 ppm), and TAA - <0.01 – 0.028 ppm (controls <0.01-0.037 ppm). The petitioner stated that the source of the TA (apple and soybean) and TAA (soybean) residues in/on the control samples was unknown, but was likely to be of natural origin and unrelated to the triazole-class pesticides. Based on the soybean TA and TAA treated to control residue ratios of 0.11-6.44 (average = 2.29) and 0.58-12.4 (average = 1.36), flutriafol may degrade to these compounds in soybean; however, for apple, there was not a significant difference between TA residue in treated and control samples (residue ratios of 0.38-2.51; average = 1.21). HED notes that samples of forage and hay were not collected from the soybean field trials and that these data are not required because the petitioner is proposing a feeding/grazing restriction for soybean. Based on the apple and soybean field trial data and the maximum residue limit (MRL) tolerance calculator, the following tolerances for residues of flutriafol *per se* are appropriate: apple - 0.20 ppm and soybean seed - 0.35 ppm. **A revised Section F is requested.**

Magnitude of the Residue - Apple and Soybean Processed Commodities: Pending submission of supporting storage stability data for T, TA, and TAA in/on aspirated grain fractions (AGF) and soybean processed commodities, the submitted apple and soybean processing studies are acceptable. The studies reflect application of flutriafol at 1.5x and 5.2x the proposed seasonal rate for apple and soybean (note that the soybean AGF residue data were generated using a 1.0x rate). Samples were analyzed for flutriafol, T, TA, and TAA using acceptable methods (flutriafol residues were >LOQ in/on the RAC). The processing data resulted in the following flutriafol processing factors (see residue chemistry summary memo (D340513) for T, TA, and TAA processing factors): apple juice - 0.5x; wet apple pomace - 1.8x; soybean meal - 1.4x; soybean hull - 1.0x; soybean oil - 1.3x; and soybean AGF - <7.4x. Based on the highest-average field trial (HAFT) flutriafol *per se* residues in apple (0.123 ppm) and soybean seed (0.303 ppm) and the processing factors, expected residues in wet apple pomace, soybean meal, soybean hull, soybean oil, and soybean AGF would be 0.22 ppm, 0.42 ppm, 0.30 ppm, 0.39 ppm, and 2.24 ppm, respectively. Based on the HED-recommended apple (0.20 ppm) and soybean seed (0.35 ppm) tolerances, HED concludes that tolerances in/on wet apple pomace, soybean meal, soybean hull, and soybean oil are unnecessary. However, HED concludes that a tolerance for residues of flutriafol *per se* of 2.2 ppm in/on AGF is appropriate. **A revised Section F is requested.**

Magnitude of the Residue - Rotational Crops: The petitioner submitted a confined rotational crop study, but this study was determined to be inadequate (see Section 5.1.2). The petitioner submitted two field rotational crops studies, which monitored for residues of flutriafol, TA, and TAA following a single bare soil incorporated application at 16x the proposed soybean application rate (studies conducted in the UK). Wheat (same year as application) or sugar beet (24 months after application) were planted and grown to maturity (residue data were not presented for these crops); the sites were planted 34-36 months after application with the rotational crops corn, potato, sunflower, sugar beet, barley, cabbage, carrot, pea, rapeseed, and wheat (sugar beet was planted 24-30 months after application). Residues of TA and TAA were found in/on many of the crops (TA: <0.05-17.0 ppm; TAA: <0.05-0.84 ppm; see residue chemistry summary memo (D340513) for details). Residues of flutriafol were also found in/on many of the samples. Normalizing the residues to 1x the soybean rate and assuming a LOQ of 0.01 ppm, quantifiable residues in/on cabbage (≤0.008 ppm), carrot root (≤0.008 ppm), sugar beet tops (≤0.026 ppm), corn straw (i.e., stover; ≤0.020 ppm), barley straw (≤0.097 ppm), wheat straw (≤0.161 ppm), and pea hay (≤0.245

ppm) may be expected.

Excluding instances where phytotoxicity is an issue, HED considers a maximum 12-month plant back interval (PBI) to be practical. If the limited field rotational crop study demonstrates quantifiable residues at 12 months, then extended field trial data are required for each desired rotational crop/PBI and tolerances are established based on these data. Note that the limited rotational crop data are conducted on root, leafy vegetable, and cereal grain crop as these are the HED-accepted surrogates for all rotational crops. In the current instance, the limited field rotational crop study indicates that quantifiable residues of flutriafol may be present in a root crop, leafy vegetable, and cereal grain planted 34-36 months following application at 1x the proposed soybean application rate. Therefore, a PBI where residues in rotational crops are <LOQ has not been demonstrated and HED does not have sufficient data to estimate residues or establish tolerance in rotational crops at any PBI. HED notes that although the nature of the residue in rotational crops has not been defined, it is convention for HED to include parent as a residue of concern in all matrices.

The petitioner has indicated that they have conducted new confined and field (limited and extended; 1x) rotational crop studies and that these data will be submitted to HED in the summer of 2009. **Since these data are forthcoming and based on the currently available data, the label should indicate that only soybean may be rotated to a treated field; a revised Section B is requested. If the petitioner would like to rotate to crops other than soybean, then confined and field rotational crop studies should be submitted as specified in OPPTS 860.1850 and OPPTS 860.1900.**

Magnitude of the Residue - Livestock: The livestock MRDBs are 0.207 ppm for beef cattle, 0.187 ppm for dairy cattle, 0.088 ppm for poultry, and 0.052 ppm for swine. The petitioner submitted a livestock feeding study (47090450.der.doc; hen, cow, hog, and sheep) which was found to be unacceptable for several reasons, including that the livestock were dosed for only 7 days rather than 28 days as specified in OPPTS 860.1480. Subsequently, the petitioner submitted dairy cattle (beef/dairy - 2.4x/2.7x, 7.2x/8.0x, and 24x/27x) and hen (5.1x, 15x, and 51x) feeding studies (hen and cattle dosed for 29 consecutive days). Provided the petitioner submits data validating the storage intervals for liver (cattle and poultry) and kidney (cattle), these studies will be classified as scientifically acceptable (stability data for flutriafol, 1,2,4-T, TA, and TAA are needed). The poultry study resulted in flutriafol *per se* residues of <LOQ in all commodities except for egg (0.0216-0.0448 ppm; avg = 0.0295 ppm), fat (0.0545-0.0717 ppm; avg = 0.0634 ppm), and liver (0.0333-0.0978 ppm; avg = 0.0657 ppm) collected from the 51x dosing group. Normalizing the average residues to 1x the MRDB results in residues of ≤0.0013 ppm. Residues of T, TA, and TAA were <LOQ in/on all matrices. The cattle study resulted in flutriafol *per se* residues of <LOQ in all commodities except for liver samples collected from the 2.4x (<0.01-0.040 ppm; avg = 0.0249 ppm), 7.2x (0.0896-0.0973 ppm; avg = 0.0934 ppm), and 24x (0.225-0.386 ppm; avg = 0.279 ppm) dosing groups. Normalizing the average residues to 1x the MRDB results in residues of 0.010-0.013 ppm. Residues of T, TA, and TAA were <LOQ in/on all matrices.

Based on the acceptable dairy cattle and hen feeding studies, HED concludes that a tolerance for residues of flutriafol *per se* in/on liver (cattle, goat, horse, and sheep) of 0.02 ppm is appropriate. HED notes that the results of the unacceptable livestock feeding study do not indicate that a ruminant liver tolerance >0.02 ppm is required or that tolerances on the remaining livestock commodities are required.

Proposed and HED-Recommended Tolerances: Tolerances are established for residues of flutriafol, including its metabolites and degradates, in or on the commodities listed below. Compliance with these tolerance levels is to be determined by measuring only flutriafol. A revised Section F is requested which indicates the Chemical Abstracts Service (CAS) chemical name for flutriafol and reflects the correct commodity definition and/or numerical tolerance specified in Table 5.1.10.1. **A revised Section F is requested.**

Table 5.1.10.1. Tolerance Summary for Flutriafol.

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Apple	0.2	0.20	Numerical tolerance should be 0.20.
Soybean	0.3	0.35	Based on the field trial data and the tolerance calculator, the numerical tolerance should be 0.35 ppm and the correct commodity definition is "Soybean, seed."
Soybean, aspirated grain fractions	0.5	2.2	Based on the field trial and processing data, the numerical tolerance should be 2.2 ppm and the correct commodity definition is "Grain, aspirated fractions."
Liver (cattle, goat, hog, horse, sheep)	0.01	--	Incorrect commodity definition.
Cattle, liver	--	0.02	--
Goat, liver	--	0.02	--
Hog, liver	--	0.02	--
Horse, liver	--	0.02	--
Sheep, liver	--	0.02	--
Eggs	0.01	--	Tolerance not required.

5.1.11 International Residue Limits

No Codex, Canadian, or Mexican MRLs have been established for flutriafol; therefore, harmonization is not an issue for this petition.

5.2 Dietary Exposure and Risk

The ROCKS concluded that based on the toxicity of the residues of concern, three risk assessments are necessary when evaluating the exposure resulting from application of flutriafol (flutriafol and M1B; T; and TA/TAA).

T and TA/TAA: T and TA/TAA are common metabolites of many triazole derivative fungicides and HED has recently conducted a dietary risk assessment for T and TA/TAA (D355015, M. Doherty, 6-Oct-2008). The resulting acute and chronic exposures to T and TA/TAA were less than HED's level of concern (T: ≤36% aPAD and ≤54% cPAD; TA/TAA: 34% aPAD and ≤40% cPAD). HED concludes that revised T and TA/TAA dietary risk assessments are unnecessary for the following reasons: **(1)** incorporation of the flutriafol uses resulted in negligible changes to the T and TA/TAA residue estimates incorporated into the previous dietary analyses and **(2)** the T and TA/TAA drinking water estimates incorporated into the previous dietary analyses assumed an annual fungicide application rate of 10.38 lb ai/acre for nonagricultural uses and 2.0 lb ai/acre for agricultural uses and the formation of T and/or TA/TAA at 30.7% of the applied rate (EFED memo; D320682, I. Maher, 28-Feb-2006). Since

the annual application rate for flutriafol is ≤0.63 lb ai/acre and since all environmental degradates were identified at <10% TRR, a revised drinking water assessment is unnecessary.

Flutriafol and M1B: Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted for flutriafol using DEEM-FCID™ (ver 2.03), which incorporates food consumption data from the USDA CSFII (1994-1996 and 1998). The residue of concern in apple and soybean seed for tolerance enforcement and risk assessment is flutriafol *per se*; the residue of concern in ruminants for tolerance enforcement is flutriafol *per se* and for risk assessment is flutriafol and M1B.

The acute and chronic analyses assumed tolerance level apple and soybean residues and modeled drinking water estimates. Since the apple processing study did not indicate a concentration of flutriafol residues in apple juice, the DEEM (ver 7.81) apple juice default processing factor was reduced to 1; the DEEM (ver 7.81) default dried apple processing factor was retained since processing data for dried apple were not provided. As indicated above, the residues of concern in ruminants for risk assessment are flutriafol and M1B (feeding study did not monitor for residues of M1B). Residues of M1B were found at 1% TRR in liver collected from the ruminant liver metabolism study (47090443.der.doc); therefore, adjustment of the ruminant liver tolerance to include residues of M1B is unnecessary. M1B was included as a residue of concern in ruminants as it was the major residue in kidney (M1B - ~23% TRR; flutriafol - 7% TRR; M1B <4% TRR in the remaining analyzed matrices). The ruminant feeding study resulted in flutriafol *per se* residues of <0.01 ppm (<LOQ) in kidney following dosing at 24x. Based on this, a ruminant kidney flutriafol *per se* tolerance was not established. Combined flutriafol and M1B kidney residues of 0.002 ppm were calculated ((0.01 ÷ 24) + (0.01 x 3.3 ÷ 24) = 0.002 ppm), assuming LOQ flutriafol residues and the flutriafol to M1B kidney residue ratio from the metabolism study. This kidney residue estimate was incorporated into the acute and chronic analyses.

5.2.1 Acute Dietary Risk Characterization

The acute (food + water) exposure risk estimate for females 13-49 years old was 3.7% aPAD at the 95th percentile of the exposure distribution. The acute (food + water) exposure estimates were <100% aPAD for the U.S. general population (<1.0% aPAD) and all population sub-groups; the most highly exposed population subgroup was infants (<1 year old) with <1.0% aPAD. Therefore, acute dietary exposure to flutriafol is not of concern to HED.

5.2.2 Chronic Dietary Risk Characterization

The chronic (food + water) exposure estimates were <100% cPAD for the U.S. general population (1.0% cPAD) and all population sub-groups; the most highly exposed population subgroup was children 1-2 years old with 4.6% cPAD. Therefore, chronic dietary exposure to flutriafol is not of concern to HED.

Table 5.2.1. Summary of the Acute and Chronic Dietary Exposure and Risk.

Population	aPAD (mg/kg/day)	Exposure (mg/kg/day)[1]	%aPAD	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
General U.S. Population	2.5	0.003661	<1.0	0.05	0.000514	1.0
All Infants (<1 year old)		0.012649	<1.0		0.002138	4.3
Children 1-2 years old		0.009584	<1.0		0.002280	**4.6**
Children 3-5 years old		0.006915	<1.0		0.001574	3.1

Table 5.2.1. Summary of the Acute and Chronic Dietary Exposure and Risk.						
Population	aPAD (mg/kg/day)	Exposure (mg/kg/day)[1]	%aPAD	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
Children 6-12 years old		0.003834	<1.0		0.000715	1.4
Youth 13-19 years old		0.002635	<1.0		0.000372	<1.0
Adults 20-49 years old		0.002724	<1.0		0.000326	<1.0
Adults 50+ years old		0.002410	<1.0		0.000313	<1.0
Females 13-49 years old	0.075	0.002773	**3.7**		0.000333	<1.0

[1] 95th percentile (tier 1 analysis)

5.2.3 Leaching of Flutriafol to Groundwater

EFED has reviewed a field leaching study conducted in Germany (Zeitz, 2009). In this study, a field, which was demonstrated to be vulnerable to leaching, was treated with 2 applications of flutriafol at 0.11 lb ai/acre; the resulting flutriafol pore water concentration was 2.9 ppb. Assuming proportionality, a pore water estimate of 8.8 ppb can be calculated for application at the maximum proposed rate (6 x 0.11 lb ai/acre). Pore water is expected to represent a worst case estimate of ground water concentration as it represents the concentration in water prior to reaching the water table where mixing with water from untreated areas will occur.

HED's acute and chronic dietary exposure analyses assumed water concentrations of 48.5 ppb and 5.7 ppb, respectively, and yielded exposure estimates of ≤3.7% aPAD and ≤4.6% cPAD. For the following reasons, HED concludes that the information attained from the prospective groundwater will not have a significant effect on the dietary exposure estimates resulting from the proposed use: (1) for the reasons listed above, pore water concentrations are considered a conservative estimate of concentrations in groundwater; (2) the water estimate incorporated into the acute analysis is greater than the estimated pore water concentration; (3) the water estimate incorporated into the chronic analysis is 65% of the estimated pore water concentration; however, based on a commodity analysis, water contributed ≤0.8% to the cPAD; and (4) the acute and chronic exposure estimates were all <5% the PAD.

6.0 Residential (Non-Occupational) Risk

There are no existing or proposed residential uses for flutriafol. Therefore, a residential assessment was not necessary.

7.0 Aggregate Risk Assessments

Acute and chronic aggregate risks were assessed based on dietary exposure from food and drinking water sources. As there are no registered or proposed uses of flutriafol that would result in residential exposure, short- and intermediate-term aggregate risks were not assessed. A quantitative cancer aggregate risk was not needed since there was no evidence of carcinogenicity.

T and TA/TAA: As noted above, the previous T and TA/TAA dietary analyses (D350664, M. Doherty, 6-Oct-2008), which resulted in exposures less than HED's level of concern, are sufficient to account for exposure to T and TA/TAA as a result of the proposed flutriafol application. Based on this, and since the proposed use is for agricultural purposes only, HED concludes that previously calculated T and TA/TAA aggregate assessments (D359490, M. Doherty, 09-Dec-2008), which resulted in exposures less than HED's level of concern, are

sufficient to account for exposure to T and TA/TAA as a result of the proposed flutriafol application.

7.1 Acute and Chronic Aggregate Risk

Since the acute and chronic dietary assessments included food and water only, the exposures in Table 5.2.2 represent aggregate exposures. Therefore, acute and chronic aggregate risks to flutriafol are not of concern to HED.

8.0 Cumulative Risk Characterization

Flutriafol is a member of the triazole-containing class of pesticides. Although conazoles act similarly in plants (fungi) by inhibiting ergosterol biosynthesis, there is not necessarily a relationship between their pesticidal activity and their mechanism of toxicity in mammals. Structural similarities do not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate by the same, or essentially the same, sequence of major biochemical events (EPA, 2002). In conazoles, however, a variable pattern of toxicological responses is found; some are hepatotoxic and hepatocarcinogenic in mice. Some induce thyroid tumors in rats. Some induce developmental, reproductive, and neurological effects in rodents. Furthermore, the conazoles produce a diverse range of biochemical events including altered cholesterol levels, stress responses, and altered DNA methylation. It is not clearly understood whether these biochemical events are directly connected to their toxicological outcomes. Thus, there is currently no evidence to indicate that conazoles share common mechanisms of toxicity and EPA is not following a cumulative risk approach based on a common mechanism of toxicity for the conazoles. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism of toxicity, see EPA's website at http://www.epa.gov/pesticides/cumulative.

Flutriafol is a triazole-derived pesticide. This class of compounds can form the common metabolite T and two triazole conjugates (TA and TAA). To support existing tolerances and to establish new tolerances for triazole-derivative pesticides, including flutriafol, U.S. EPA conducted a human-health risk assessment for exposure to T, TA, and TAA resulting from the use of all current and pending uses of any triazole-derived fungicide. The risk assessment is a highly conservative, screening-level evaluation in terms of hazards associated with common metabolites (e.g., use of a maximum combination of uncertainty factors) and potential dietary and non-dietary exposures (i.e., high-end estimates of both dietary and non-dietary exposures). In addition, the Agency retained the additional 10X FQPA SF for the protection of infants and children. The assessment includes evaluations of risks for various subgroups, including those comprised of infants and children. The Agency's complete risk assessment is found in the propiconazole reregistration docket at http://www.regulations.gov, Docket Identification (ID) Number EPA-HQ-OPP-2005-0497.

9.0 Occupational Risk Assessment

Reference: Memo, K. Lowe, D353076, 01-JUN-2009.

Based on the proposed uses on soybeans and apples, occupational handler and post-application exposure is expected.

9.1 Occupational Handler Risk Assessment

There is potential for occupational handler exposure from the proposed uses on agricultural crops. It is anticipated that the following scenarios could result in handler exposure:

- Mixing/loading liquid concentrate to support aerial applications;
- Mixing/loading liquid concentrate to support groundboom applications;
- Mixing/loading liquid concentrate to support airblast application;
- Applying sprays with aircraft (enclosed cockpit);
- Applying sprays with groundboom equipment;
- Applying sprays with airblast equipment; and
- Flagging to support aerial spray applications.

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (August, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline," that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves, as well as for "baseline" and the use of protective gloves or other PPE as might be necessary. The flutriafol product labels direct applicators and other handlers to wear long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks.

Exposure Duration
Handler exposure is expected to be short- or intermediate-term based on information provided on proposed labels. In addition, the short- and intermediate-term toxicological endpoints are the same; therefore, the estimates of risk for short-term duration exposures are protective of those for intermediate-term duration exposures. Long-term exposures are not expected; therefore, a long-term assessment was not conducted.

Risk Calculations
A dermal-absorption factor of 21% based on an *in vivo* rat dermal-absorption study was identified and an inhalation absorption factor of 100% for extrapolation from an oral exposure to an inhalation exposure will be assumed. A body weight of 60 kg was used since the endpoints were from developmental toxicity studies. The dermal and inhalation MOEs were combined for the occupational handler risk assessments because the toxicity PODs for the dermal and inhalation routes of exposure are based on the same toxicological effects.

Daily dermal or inhalation handler exposures are estimated for each applicable handler task using the following formula:

Daily Exposure (mg ai/day) = Unit Exposure (mg ai/lb ai handled) x Application Rate (lbs ai/gallon) x Amount Handled (gal/day)

Where:

Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Unit Exposure	=	Unit exposure value (mg ai/lb ai) derived from August 1998 PHED data or from ORETF data;
Application Rate	=	Normalized application rate (lb ai/gal); and
Daily Area Treated	=	Normalized amount handled (gal/day).

The daily dermal or inhalation dose is calculated by normalizing the daily exposure by body weight and adjusting, if necessary, with an appropriate dermal or inhalation absorption factor using the following formula:

Average Daily Dose (mg/kg/day) = Daily Exposure (mg ai/day) x (Absorption Factor (%/100) / Body Weight (kg)

Where:

Average Daily Dose	=	Absorbed dose received from exposure to a pesticide in a given scenario (mg ai/kg bw/day);
Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Absorption Factor	=	A measure of the amount of chemical that crosses a biological boundary such as the skin or lungs (% of the total available absorbed); and
Body Weight	=	Body weight determined to represent the population of interest in a risk assessment (kg).

Non-cancer dermal and inhalation risks for each applicable handler scenario are calculated using a MOE, which is a ratio of the POD to the daily dose. All MOE values were calculated using the formula below:

MOE= POD (mg/kg/day) / Average Daily Dose (mg/kg/day)

A total MOE was calculated because the dermal and inhalation toxicological PODs are based on the same adverse effects. The total MOE values were calculated using the formula below:

Total MOE = 1 / [(1/dermal MOE) + (1/inhalation MOE)]

Table 9.1 presents the exposure/risks for short and intermediate-term dermal and inhalation exposures at baseline, and with additional PPE. The combined dermal and inhalation exposure risks for mixer/loaders are not of concern (i.e., MOEs >100), **provided the mixer/loaders wear protective gloves as directed on the label.**

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); pilots are not required to wear protective gloves. With this level of protection, there are no risks of concern for applicators.

Table 9.1. Agricultural Handler Exposure and Risk for Flutriafol.

Exposure Scenario	Application Rate (lb ai/acre)	Area Treated Daily (acres)	Unit Exposures			Dose (mg/kg/day)					MOE				
			Baseline Dermal (mg/lb ai)	Baseline Inhalation (ug/lb ai)	PPE-G Dermal (mg/lb ai)	Baseline Dermal	Baseline Inhalation	PPE-G Dermal	Combined Baseline Dermal + Baseline Inhalation	PPE-G Dermal + Baseline Inhalation	Baseline Dermal	Baseline Inhalation	PPE-G Dermal	Combined Baseline Dermal + Baseline Inhalation	Combined PPE-G Dermal + Baseline Inhalation
Mixer/Loader															
Mixing/Loading Liquids for Aerial Applications	0.11	1200	2.9	1.2	0.023	1.3	0.0026	0.011	1.30	0.0130	**6**	2,800	710	**5.6**	570
Mixing/Loading Liquidss for Groundboom Applications	0.11	200	2.9	1.2	0.023	0.22	0.00044	0.0018	0.22	0.0022	**34**	17,000	4,200	**34**	3,400
Mixing/Loading Liquids for Airblast Applications	0.11	40	2.9	1.2	0.023	0.045	0.000088	0.00035	0.05	0.00044	170	85,000	21,000	170	17,000
Applicator															
Applying Sprays via Aerial Equipment	0.11	1200	0.005 (eng control)	0.068 (eng control)	No Data	0.0023 (eng control)	0.00015 (eng control)	No Data	0.0025 (eng control)	No Data	3,200 (eng control)	50,000 (eng control)	No Data	3,000 (eng control)	No Data
Applying Sprays via Groundboom Equipment	0.11	200	0.014	0.74	0.014	0.0011	0.00027	0.0011	0.0013	0.0013	7,000	28,000	7,000	5,600	5,600
Applying Sprays via Airblast Equipment	0.11	40	0.36	4.5	0.24	0.0055	0.00033	0.0037	0.0059	0.004	1,400	23,000	2,000	1,300	1,900
Flagger															
Flagging for Aerial Sprays Applications	0.11	350	0.011	0.35	Not applicable	0.0015	0.00022	Not applicable	0.0017	Not applicable	5,100	33,000	Not applicable	4,400	Not applicable

1. Application Rates based on proposed uses on label for flutriafol product TOPGUARD™ (EPA 67760-xxx).
2. Science Advisory Council for Exposure (ExpoSAC) Policy # 9.1.
3. Unit Exposures based on PHED Version 1.1. Baseline Dermal: Long-sleeve shirt, long pants, and no gloves. Baseline Inhalation: no respirator. PPE-G: Baseline plus chemical-resistant gloves. Eng control: engineering control for applying sprays via aerial equipment = enclosed cockpit.
4. Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/acre) x acres treated x absorption factor (dermal: 21%; inhalation: 100%) / body weight (60 kg adult female).
5. Combined dose (mg/kg/day) = Dermal dose (mg/kg/day) + Inhalation dose (mg/kg/day).
6. MOE = POD (NOAEL, 7.5 mg/kg/day) / Dose (mg/kg/day) and Combined MOE = POD (NOAEL, 7.5 mg/kg/day) / combined dose (mg/kg/day).

9.2 Occupational Post-application Exposure

HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Since flutriafol is applied only in outdoor settings and has a low vapor pressure, post-application inhalation exposures and risks were not assessed.

There is a potential for post-application exposure to field workers following foliar application of flutriafol to agricultural crops. Post-application exposure is expected to be short- or intermediate-term based on information provided on proposed labels. In addition, the short- and intermediate-term toxicological endpoints are the same; therefore, the estimates of risk for short-term duration exposures are protective of those for intermediate-term duration exposures. Since no post-application data were submitted in support of this registration action, dermal exposures during post-application activities were estimated using dermal transfer coefficients (TCs) from the ExpoSAC Policy Number 3.1: Agricultural TCs, August 2000, summarized in Table 9.2.1 below and the following assumptions:

Application Rate = 0.11 lb ai/A
Exposure Duration = 8 hours per day
Body Weight = 60 kg for adult female
Dermal Absorption = 21%
Fraction of a.i. retained on foliage is assumed to be 20% (0.2) on the day of application (= % dislodgeable foliar residue, DFR, after initial treatment) for agricultural crops. This fraction is assumed to further dissipate at the rate of 10% (0.1) per day on following days. These are default values established by HED's ExpoSAC.

Table 9.2.1. Anticipated Post-application Activities and Dermal TCs.

Proposed Crops	Policy Crop Group Category	Transfer Coefficients (cm^2/hr)	Activities
Apples	Tree, fruit, deciduous	3,000	Thinning
		1,500	Hand harvesting, propping, hand pruning, training
		1,000	Scouting and hand weeding and irrigating
Soybeans	Field row crop, low/medium	1,500	Scouting and irrigating
		100	Scouting and hand weeding

The following equations were used to calculate risks for workers performing post-application activities:

$$DFR_t = AR \times F \times (1-D)^t \times CF1 \times CF2$$

Where:
DFR_t = dislodgeable foliage residue on day "t" ($\mu g/cm^2$)
AR = application rate (lb ai/acre)
F = fraction of ai retained on foliage (unitless)
D = fraction of residue that dissipates daily (unitless)

CF1 = conversion factor, 4.54E8 µg/lb
CF2 = conversion factor, 2.47E-8 acre/cm^2

and

$$Daily\ dermal\ dose_t = (DFR_t \times CF1 \times TC \times DA \times ET) / BW$$

Where:

Daily dermal dose	=	Absorbed dose received from exposure to a pesticide in a given scenario on day "t" (mg/kg/day)
DFR_t	=	dislodgeable foliage residue on day "t" (µg/cm^2)
CF1	=	conversion factor, 1E-3 mg/µg
TC	=	transfer coefficient (cm^2/hr)
DA	=	dermal-absorption factor (unitless)
ET	=	exposure time (hr/day)
BW	=	body weight (kg)

and

$$MOE = POD\ (mg/kg/day) / Daily\ Dermal\ Dose\ (mg/kg/day)$$

The post-application exposures associated with the proposed uses are summarized in Table 9.2.2. The resulting MOEs are greater than 100 on day 0 (12 hours after application) and, therefore, do not exceed HED's LOC.

Table 9.2.2. Post-application Exposure and Risk for Flutriafol.

Crop Grouping/Crop	Activity	Transfer Coefficient	Days after Treatment	DFR[1] (µg/cm^2)	Daily Dermal Dose[2] (mg/kg/day)	MOE[3]
Tree Fruit, Apples	Thinning	3,000	0 (12 hours)	0.25	0.021	360
	Hand harvesting, hand pruning, training, propping	1,500			0.010	720
	Scouting, hand weeding, irrigating	1,000			0.007	1100
Field and row crops, soybeans	Scouting and irrigating	1,500			0.010	720
	Scouting and hand weeding	100			0.0007	11,000

1 DFR = application rate (0.11 lb ai/A) x (1- daily dissipation rate) ^{t} x 4.54E8 µg/lb x 24.7E-9 A/cm^2 x 20% DFR after initial treatment.

2 Daily Dermal Dose = [DFR (µg/cm^2) x TC x 0.001 mg/µg x 8 hrs/day x 21% dermal absorption] ÷ body weight (60 kg adult female).

3 MOE = POD (NOAEL, 7.5 mg/kg/day) / Daily Dose.

9.3 REI

Since post-application risks were not a concern on day 0 (12 hours following application), the REI is based on the acute toxicity of flutriafol technical material which is classified as Category III for eye irritation potential and Category IV for skin irritation potential. Flutriafol is classified as Category II for acute dermal toxicity based on an absence of systemic toxicity at 1000 mg/kg/day in the 28-day dermal toxicity study in the rat. Flutriafol is not a dermal sensitizer. Under the Worker Protection Standard for Agricultural Pesticides, active ingredients classified as acute Toxicity Category II are assigned a 24-hour REI. Therefore, the 12-hour REI that appears on the proposed label needs to be corrected to 24 hours.

10.0 Data Needs and Label Recommendations

Toxicology

- **Immunotoxicity Study.** An immunotoxicity study is now a data requirement in the 40 CFR revised Part 158.

Residue Chemistry

- Submission of flutriafol analytical standard to ACL.
- A revised Section B with the following changes is requested: **(1)** the proposed minimum apple RTI of 7 days for apples is not supported by the crop field trial data; the use directions should be revised to specify a minimum apple RTI of 14 days; **(2)** the apple use directions should be amended to specify a minimum spray volume of >20 GPA; **(3)** since the soybean and apple field trials did not include an adjuvant, the label should be revised prohibiting the addition of adjuvants to the spray solutions; **(4)** the soybean use directions should be limited to the application to soybeans harvested for the dried seed; and **(5)** the label should indicate that only soybean may be rotated to a treated field.
- Revised Section F. Tolerances are established for residues of flutriafol, including its metabolites and degradates, in or on the commodities listed below. Compliance with the following tolerance levels is to be determined by measuring only flutriafol [(±)-α-(2-fluorophenyl)-α-(4-fluorophenyl)-1*H*-1,2,4-triazole-1-ethanol]:

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Apple	0.2	0.20	Numerical tolerance should be 0.20.
Soybean	0.3	0.35	Based on the field trial data and the tolerance calculator, the numerical tolerance should be 0.35 ppm and the correct commodity definition is "Soybean, seed."
Soybean, aspirated grain fractions	0.5	2.2	Based on the field trial and processing data, the numerical tolerance should be 2.2 ppm and the correct commodity definition is "Grain, aspirated fractions."
Liver (cattle, goat, hog, horse,	0.01	--	Incorrect commodity definition.
Cattle, liver	--	0.02	--
Goat, liver	--	0.02	--
Hog, liver	--	0.02	--

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Horse, liver	--	0.02	--
Sheep, liver	--	0.02	--
Eggs	0.01	--	Tolerance not required.

- Information concerning the storage conditions/interval for the samples collected from the ruminant metabolism study; if the storage intervals were >6 months, then data demonstrating the stability of the metabolic profile in the various matrices will be required.
- Submission of storage stability data demonstrating the stability of T, TA, and TAA in the soybean matrices for the employed intervals (soybean seed - 16 months; soybean meal, hull, and oil - 12 months).
- Storage stability data for flutriafol, T, TA, and TAA in ruminant liver (139 days).

Occupational and Residential Exposure

- Change the REI on the proposed label from 12 hours to 24 hours.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for food use for flutriafol are in Table 1. Use of the new guideline numbers does not imply that the new (post-1998) guideline protocols were used.

Table 1. Toxicology Data Requirements for Flutriafol

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	no
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5400	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5500	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neurotoxicity	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
870.7800	Immunotoxicity	yes	no
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	-
	Subchronic Oral (rat)	no	-
	Six-month Oral (dog)	no	-

A.2. Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Flutriafol.				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral (rat)	47090336	LD_{50} = 1140 mg/kg (M); 1480 mg/kg (F)	III
870.1200	Acute dermal (rat)	47090337	-	II[1]
870.1300	Acute inhalation (rat)	47090338	LC_{50} > 5.20 mg/L	IV
870.2400	Primary eye irritation (rabbit)	47090339	Minimally irritating	III
870.2500	Primary dermal irritation (rabbit)	47090341	Not a dermal irritant	IV
870.2600	Dermal sensitization (mouse)	47090343	Not a sensitizer	-

[1] Category II, based on no toxicity observed up to 1000 mg/kg/day in the 28-day dermal toxicity study in rat.

Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Flutriafol.			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3050	28-Day oral toxicity (rat)	47090344 (1982) Acceptable/non-guideline 0, 100, 300, 800, 2000, or 5000 ppm (0, 10, 30, 80, 200, and 500 mg/kg/day)	NOAEL = 800 ppm (80 mg/kg/day) LOAEL = 2000 ppm (200 mg/kg/day), based on liver toxicity (increased weight, centrilobular hepatocellular hypertrophy, fatty change, hydropic degeneration, smooth endoplasmic reticulum proliferation, and increased aminopyrine-N-demethylase activity) in both sexes and decreased body-weight gain and food consumption in males.
870.3100	90-Day oral toxicity (rat)	47090345 (1982) Acceptable/guideline 0, 20, 200, or 2000 ppm M: 0, 1.5, 14, and 158 mg/kg/day) F: 0, 1.6, 22, and 145 mg/kg/day	NOAEL = 200 ppm (14/22 mg/kg/day in M/F) LOAEL = 2000 ppm (158/145 mg/kg/day in M/F), based on decreased body-weight gain, decreased food consumption and liver toxicity (increased absolute and adjusted liver weights, increased endoplasmic reticulum proliferation in the males, and increased APDM activity).
870.3150	90-Day oral toxicity (dog)	47090346 (1982) Acceptable/guideline 0, 1, 5, or 15 mg/kg bw/day	NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day, based on adverse liver findings (increases in organ weight, alkaline phosphatase, aminopyrine N-demethylase activity, and incidence of hemosiderin-laden Kupffer cells) in both sexes, spleens with hemosiderin content slightly higher than controls in the males, and decreased cumulative body-weight gains and increased triglycerides in the females.
870.3200	28-Day dermal toxicity (rat)	47090347 (2007) Acceptable/guideline 0, 250, 500, or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL was not established
870.3700a	Prenatal developmental (rat)	47090349 (1982) Unacceptable/guideline 0, 10, 50, or 125 mg/kg/day	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 125 mg/kg/day, based on increased incidence of ventral/genital staining of the fur and decreased maternal body-weight gains and food consumption. **Developmental** NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day, based on delayed ossification or non-ossification of the skeleton in the fetuses.

Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Flutriafol.			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a	Prenatal developmental (rat)	47521303 (2008) Acceptable/guideline 0, 2, 5, 10, or 755 mg/kg/day	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 75 mg/kg/day, based on decreased body-weight gains and food consumption. **Developmental** NOAEL = 10 mg/kg/day LOAEL = 75 mg/kg/day, based on increased late resorptions; malformations (cleft palate and multiple hyoid malformations) and variations in the hyoid; variations in the maxilla/mandible, rudimentary and long cervical ribs, pelvic girdle, and radius/ulna; numerous skeletal retardations detailed above and corresponding decrease in fetal weights.
870.3700b	Prenatal developmental (rabbit)	47090350 (1982) Acceptable/guideline 0, 2.5, 7.5, or 15 mg/kg/day	**Maternal** NOAEL = 7.5 mg/kg/day LOAEL = 15 mg/kg/day, based on decreased corrected and uncorrected body-weight gains and food consumption. **Developmental** NOAEL = 7.5 mg/kg/day LOAEL = 15 mg/kg/day, based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss.
870.3800	2-gen. reproduction and fertility effects (rat)	47090351 (1986) Acceptable/guideline 0, 60, 240 or 1,000 ppm M: 0, 4.8, 20.6 and 88.7 mg/kg/day) F: 0, 5.5, 21.9, and 103 mg/kg/day	**Parental/Systemic** NOAEL = 240 ppm (20.6/21.9 mg/kg/day [M/F]) LOAEL = 1000 ppm (88.7/103 mg/kg/day [M/F]) based on decreased body-weight gains and food consumption and on effects on the liver (increased liver weights, centrilobular hypertrophy, and fatty change). **Reproductive** NOAEL = 1000 ppm (88.7/103 mg/kg/day [M/F]) LOAEL was not determined. **Offspring** NOAEL = 240 ppm (20.6/21.9 mg/kg/day [M/F]) LOAEL = 1000 ppm (88.7/103 mg/kg/day [M/F]) based on decreased live birth index and litter size and on effects on the liver (fatty change/vacuolation).

Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Flutriafol.			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100	Chronic toxicity (1 year; dog)	47090353 (1988) Acceptable/guideline 0, 1, 5, or 20 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 20 mg/kg/day, based on: adverse liver findings (increased liver weights, increased centrilobular hepatocyte lipid in the liver, and increases in alkaline phosphatase, albumin and triglycerides), increased adrenal cortical vacuolation of the zona fasciculata, and marked hemosiderin pigmentation in the liver and spleen in both sexes; mild anemia (characterized by decreased hemoglobin, hematocrit, and red blood cell count) in the males; and initial body weight losses, decreased cumulative body-weight gains, and increased adrenal weights in the females.
870.4200	Carcinogenicity (mouse)	47090354 (1988) Acceptable/guideline 0 (two control groups), 10, 50, or 200 ppm M: 0, (0, 1.1, 5.9, and 24 mg/kg/day) F: 0, 1.4, 7.4, and 31 mg/kg/day	NOAEL = 50 ppm (5.9/7.4 mg/kg/day in M/F) LOAEL = 200 ppm (24/31 mg/kg/day in M/F), based on hepatotoxicity (increased fatty change) in both sexes. No evidence of carcinogenicity.
870.4300	Combined Chronic Toxicity/ Carcinogenicity (rat)	47090352 (1986) Acceptable/guideline 0, 20, 200, or 2000 ppm M: 0, 1.02, 10.0, and 102 mg/kg/day) F: 0, 1.27,12.2, and 122 mg/kg/day	NOAEL = 200 ppm (10.0/12.2 mg/kg/day in males/females) LOAEL = 2000 ppm (102/122 mg/kg/day in males/females), based on adverse liver effects (increased liver weights, fatty change, bile duct proliferation/cholangiolarfibrosis, hemosiderin accumulation in Kupffer cells and centrilobular hypertrophy), and clinical chemistry findings. No evidence of carcinogenicity.
870.5100	*In vitro* Bacterial Gene Mutation *(Salmonella typhimurium)*/ mammalian activation gene mutation assay	47090401 (1988) Acceptable/guideline 0, 1.6, 8, 40, 200, 1000, or 5000 µg/plate (Trial 1) or 0, 8, 40, 200, 1000, 2500, or 5000 µg/plate (Trial 2); Both trials were performed w/wo S9-activation	There were no marked increases in the mean number of revertants/plate in any strain. There was no evidence of induced mutant colonies over background.

Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Flutriafol.			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5300	*In Vitro* Gene Mutation assay in mouse lymphoma cells	47090402 (1986) Acceptable/guideline 0, 10, 33, 100, 333, or 1000 µg/mL (+S9, Trial 1); 0, 150, 300, 450, 600, or 750 µg/mL (-S9, Trial 1); 0, 150, 300, 450, 600, 750, 900, 1050, or 1200 µg/mL (+S9, Trial 2); or 0, 200, 300, 400, 500, 600, 700, or 800 µg/mL (-S9, Trial 2)	There was a dose-related increase in mutant frequency (7.0-9.0x10^{-5} treated vs. 3.0x10^{-5} controls) and absolute mutant numbers (70-148 colonies/plate vs. 63 controls) at 100 µg/mL and above in Trial 1 and a marked increase in mutant frequency at 750 µg/mL (6.5x10^{-5} treated vs. 1.2x10^{-5} controls) in Trial 2 attributable to severe cytoxicity (2% relative survival). However, the increases in mutant frequency did not achieve the threshold value for a positive response (>10x10^{-5}) in either trial and there was no marked increase in absolute mutant numbers at 750 µg/mL in Trial 2. In the absence of S9, there were no marked increases in mutant frequency or absolute mutant numbers compared to controls in either trial. There was no convincing evidence of induced mutant colonies over background in the presence or absence of S9-activation.
870.5375	*In vitro* Mammalian Cytogenetics (Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes)	47090403 (1989) Acceptable/guideline 0, 25, 125, or 250 µg/mL (+/-S9)	No significant increases in the numbers of cells with aberrations (excluding gaps) were observed in either donor in the presence or absence of S9. There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation.
870.5385	*In vivo* Mammalian Cytogenetics – [Bone Marrow Chromosomal Aberration Test	47090404 (1982) Acceptable/guideline 0, 15, 70, or 150 mg/kg	There was no evidence of chromosome aberration induced over background.
870.5395	*In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in Mice	47090405 (1986) Acceptable/guideline 0, 93.8, or 150 mg/kg	Decreased ($p<0.01$) polychromatic erythrocyte to normochromatic erythrocyte ratios (PCE:NCE) were observed in both doses at all time points, indicating that the test material was toxic to the bone marrow. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.
870.5450	Dominant Lethal Assay - Mice	47090406 (1982) Acceptable/guideline 0, 25, 50, or 100 mg/kg/day (total doses of 0, 125, 250, or 500 mg/kg)	Mortality (3/15 males) was noted at 100 mg/kg/day during dosing. Slight decreases ($p<0.05$) in body weight were observed at 50 mg/kg/day and above during dosing. There were no treatment-related effects on fertility, mean number of implantations, or the number of early or late deaths. There was no time-related positive response of increased pre- or post-implantation loss compared to controls.

Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Flutriafol.			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5550	Unscheduled DNA Synthesis in Primary Rat Hepatocytes/Mammalian Cell	47090407 (2003) Acceptable/guideline 0, 250, 500, or 1000 mg/kg	The net nuclear grain (NNG) counts in the treated animals (–3.42 to –2.64) were well below the threshold of ≥5 NNG needed for a positive response, and no increase in the mean percent of cells in repair was observed. There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.
870.6200a	Acute neurotoxicity screening battery	47090408 (2005) Acceptable/guideline 0, 125, 250, or 750 mg/kg	NOAEL = 250 mg/kg LOAEL = 750 mg/kg, based on decreased body weight, body-weight gain, absolute and relative food consumption, and clinical signs of toxicity, indicative of a moribund condition, in both sexes: dehydration, urine-stained abdominal fur, ungroomed coat, ptosis, decreased motor activity, prostration, limp muscle tone, muscle flaccidity, hypothermia, hunched posture, impaired or lost righting reflex, scant feces; in males: red or tan perioral substance, chromodacryorrhea, chromorhinorrhea and labored breathing, and in females: piloerection and bradypnea, and signs of neurotoxicity: hunched posture in females and ataxia in males.
870.6200b	Subchronic Neurotoxicity – Feeding Study in Rats	47090410 (2007) Acceptable/guideline 0, 500, 1500, or 3000 ppm (0/0, 28.9/32.6, 84.3/97.6, and 172.1/185.0 mg/kg/day [M/F])	NOAEL = 1500 ppm (84.3/97.6 mg/kg/day [M/F]). LOAEL = 3000 ppm (172.1/185.0 mg/kg/day [M/F]) based on decreased body-weight gain, absolute and relative food consumption; and decreased hindlimb grip strength in males.

Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Flutriafol.			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485	Metabolism and pharmacokinetics (rat)	47090412 (2006) Acceptable/guideline 5 or 250 mg/kg	More than 78% of the dose was recovered in the bile and urine. Absorption was similar between sexes and between single and multiple dose regimes. Absorption is extensive. The dose was mostly eliminated within 48 hours. Only 0.04-0.05% of the dose was found in the expired carbon dioxide. Most of the radioactivity was excreted in the bile (47-79% of the dose). The excretion profile was similar between sexes. In the blood, radioactivity partitioned into the red blood cells. In both sexes and all groups, concentrations of radioactivity were relatively high in whole blood, liver and kidneys. Other organs with high concentrations included the adrenal glands, spleen, and pituitary. The distribution profiles were similar between species, dose level, and single vs multiple dose regime. In the whole blood, the concentrations were proportional to the dose. The total amount of radioactivity isolated in the tissues and carcass was <1-3%. Bioaccumulation was considered unlikely. The parent was isolated in only trace amounts in the urine and feces and more than 19 metabolites were isolated, indicating extensive metabolism. Metabolism profiles were similar between sexes. The metabolic profiles were similar regardless of the matrix (feces, urine, or bile), the dose, and the sex. The primary site for metabolism was the 2-fluorophenyl ring. The initial metabolic step was epoxidation followed by either rearrangement to form the dihydrodiol isomers or to form hydroxy or dihydroxy metabolites. The hydroxyl groups on these primary metabolites may then be either conjugated with glucuronic acid or methylated. A second, minor route for metabolism of flutriafol was via the removal of the triazole ring to form 1-(2 fluorophenyl)-1-(4-fluorophenyl)-ethandiol, which is then conjugated with glucuronic acid.

Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Flutriafol.			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.7600	*In vivo* dermal penetration (rat)	47090415 (2006) Acceptable/guideline 0.02, 0.2 or 2 mg/cm^2 skin were tested (10 µl/cm^2 skin), and actual doses were 0.0208, 0.201, and 2.154 mg/cm^2 skin	Dermal ranged up to 15.8% of the applied dose. Absorption was minimal with only 4 h of exposure. Absorbable radioactivity (radioactivity in the skin at the application site and the adjacent skin) was minimal in groups that were exposed for 10 h and evaluated for an additional 158 h post-exposure. Thus, almost all of the dose isolated in the skin will be absorbed. Considering the sum of absorbable and absorbed doses, 4-37% of the applied dose was recovered in the treatment groups (11%). Absorption rate constants were calculated as 0.236, 0.190, and 0.072 h^{-1} for the 2, 20, and 200 µg/cm^2 dose groups. Absorption mechanisms were saturated at the high dose. The elimination half-lives were calculated to be 31, 30, and 37 h for the 2, 20, and 200 µg/cm^2 dose groups. A maximum of 36.56% of the applied dose was noted as absorbed/absorbable (observed after 24 h exposure to 2 µg/cm^2). The dose that is absorbed/absorbable following a 10 h exposure is 16.54%, 21.31% and 11.39%, respectively, at 2, 20 and 200 µg/cm^2.

A.3. Executive Summaries

A.3.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat

In a subchronic oral toxicity study (MRID 47090345), PP450 (93% a.i.; Batch No. P10) was administered to 20 Wistar rats/sex/dose in the diet at dose levels of 0, 20, 200, or 2000 ppm (calculated to be 0, 1.5, 14 and 158 mg/kg bw/day in males, and, 0, 1.6, 22 and 145 mg/kg/day in females) for 90 days.

No treatment-related effects were noted on mortality, clinical signs of toxicity, ophthalmoscopic examinations, urinalysis, or gross pathology at any dose in either sex.

At 2000 ppm, body-weight gains were decreased ($p<0.01$) throughout the study by 15-62% in both sexes. Food consumption was decreased ($p<0.05$) by 7-21% in the males (Weeks 1, 3, 5, 8, 10, and 12) and 9-35% in the females (throughout the study). Total (Weeks 1-13) food consumption was decreased ($p<0.01$) by 7-19% in both sexes. At 200 ppm, sporadic decreases ($p<0.05$) of 5-12% were noted in food consumption and overall food consumption was decreased by 6-7% in both sexes. At 20 ppm, sporadic decreases ($p<0.05$) in food consumption of 4-12% in was observed in both sexes.

Slight anemia was noted at 2000 ppm as indicated by decreases ($p<0.01$) in the following parameters: (i) hemoglobin (↓4-7%) at Weeks 4 and 13; (ii) hematocrit (↓5%) at Week 13; (iii) mean corpuscular volume (↓3%) at Week 13; (iv) mean corpuscular hemoglobin (↓3-4%) at Weeks 4 and 13 and (v) mean corpuscular hemoglobin concentration at Weeks 4 and 13 (↓1-3%). The kaolin-cephalin time was decreased (↓13%) at terminal sacrifice. APDM activity was increased ($p<0.05$) by 22-27% in both sexes, triglycerides were decreased ($p<0.01$), and cholesterol was increased ($p<0.01$) at Weeks 4 and 13 in both sexes.

The target organ was the liver. At 200 ppm, the absolute and adjusted liver weights were increased ($p<0.05$) in females by 5-8% at this dose. At 2000 ppm, increases ($p<0.01$) in absolute and adjusted for body weight liver weights were observed in both sexes. Increased incidence (# affected/40) of hepatocyte vacuolation (fatty change) was noted in 25 treated animals vs. 5 controls. Centrilobular hypertrophy (25 treated vs. 0 controls) with associated proliferation of smooth endoplasmic reticulum and elevated aminopyridine-N-demethylase (APDM) activity was also observed in both sexes at this dose. Smooth endoplasmic reticulum proliferation in the liver was increased ($p<0.01$) in the males.

The LOAEL is 2000 ppm (158/145 mg/kg bw/day in males/females) based on decreased body-weight gain; decreased food consumption and liver toxicity (increased absolute and adjusted liver weights, increased endoplasmic reticulum proliferation in the males, and increased APDM activity). The NOAEL is 200 ppm (14/22 mg/kg bw/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

870.3150 90-Day Oral Toxicity - Dog

In a subchronic toxicity study in dogs (MRID 47090346), Flutriafol technical (PP450; 93.0% a.i.; batch # P10) was administered to four beagle dogs/sex/dose group daily by capsule for 90 days at doses of 0, 1, 5, or 15 mg/kg/day.

No adverse, treatment-related effects were observed on mortality, clinical signs of toxicity, food consumption, ophthalmoscopic examinations, hematology, urinalysis, or gross pathology.

Mild focal alveolitis/bronchiolitis of the lungs was observed in the females at 1 (3/4 dogs), 5 (1/4 dogs), and 15 (3/4 dogs) mg/kg/day compared to (0/4) controls. However, the Sponsor stated that this finding was common in Alderley Park beagles, and was probably partly associated with migration of Ascarid larvae and partly with respiratory viruses. Additionally, there was no strong dose relationship, and this finding was observed in (2/4) control males. Therefore, this finding was considered equivocal.

The liver was a target organ. At 15 mg/kg/day, absolute and adjusted for body weight liver weights were increased ($p \leq 0.05$; except not significant [NS] for absolute weight in females) by 15-36% in both sexes. A slight increase in hemosiderin-laden Kupffer cells in the liver was observed in both the males (3/4 treated vs. 1/4 controls) and females (4/4 treated vs. 0/4 controls). Alkaline phosphatase was increased ($p \leq 0.05$) in both sexes during Weeks 4, 8, and 13 by 42-82%, and the increases became greater in magnitude with time of exposure. Triglycerides were increased ($p \leq 0.01$) by 65% in the 15 mg/kg/day females during Week 13. Hepatic aminopyrine N-demethylase activity was increased ($p \leq 0.01$) in both sexes by 149-156%.

Additionally at 15 mg/kg/day, cumulative body-weight gains in the females were decreased ($p \leq 0.05$; except NS during Weeks 2, 5, and 6) throughout treatment by 39-75%, with body weight losses of 0.3-0.5 kg occurring during Weeks 1 and 2. Additionally, males were also noted to have spleens with hemosiderin content slightly higher than controls in 3/4 dogs compared to 0 controls.

The LOAEL is 15 mg/kg/day, based on adverse liver findings (increases in organ weight, alkaline phosphatase, aminopyrine N-demethylase activity, and incidence of hemosiderin-laden Kupffer cells) in both sexes, spleens with hemosiderin content slightly higher than controls in the males, and decreased cumulative body-weight gains and increased triglycerides in the females. The NOAEL is 5 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150) for a subchronic oral toxicity study in dogs.

870.3200 21/28-Day Dermal Toxicity – Rat

In a 28-day dermal toxicity study (MRIDs 47090347 and 47090348), Flutriafol Technical (Batch # UPL Bx 1; purity 95.1% a.i.) was applied to the clipped skin of ten Sprague Dawley (Crl:CD[SD]) rats/sex at dose levels of 0, 250, 500, or 1000 mg/kg bw/day (corrected for purity) in a dose volume of 1.0 mL/kg for six hours/day on at least 28 consecutive days. Rats were sacrificed on Day 29.

No effects of treatment were observed on mortality, clinical signs of toxicity, neurobehavioral

examinations, body weights, body-weight gains, food consumption, ophthalmology, hematology, clinical chemistry, or gross or microscopic pathology.

In the 500 mg/kg/day females, increased incidence (total # observations/# of rats with observation) of erythema grade 1 (24/5; not significant [NS]) and flaking grade 1 (12/5; $p \leq 0.05$) were observed at the treatment site. Additionally at 1000 mg/kg/day, increased ($p \leq 0.01$) incidences of erythema grade 1 (52/7 males; 73/10 females), flaking grade 1 (11/6 males; 49/7 females), and scab(s) (35/5 males [NS]; 17/4 females) were noted at the treatment site.

The systemic LOAEL was not observed. The NOAEL is 1000 mg/kg bw/day (limit dose).

This 28-day dermal toxicity study is classified **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.3200) for a dermal toxicity study in the rat.

A.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 47090349), Flutriafol (PP450; 93%; Batch # P10) in corn oil was administered via daily oral gavage in a dose volume of 10 mL/kg to 24 presumed pregnant Wistar rats at doses of 0, 10, 50, or 125 mg/kg/day from gestation days (GD) 6-15. On GD 21, all dams were euthanized; each dam's uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations and variations.

All dams survived until scheduled termination. There were no treatment-related macroscopic findings.

Increased incidence of staining of the genital/ventral fur was observed primarily during the dosing period in 16 dams at 125 mg/kg/day compared to 7 dams in the control group. Additionally at 125 mg/kg/day, maternal body-weight gains were decreased ($p \leq 0.01$) during the treatment (decr. 26%) and post-treatment (decr. 33%) intervals, and for the overall study (decr. 23%). Overall net weight gain, corrected for gravid uterine weight, was decreased by 19% compared to controls. Food consumption was decreased by 14-17% at this dose compared to controls during the treatment and post-treatment intervals.

The maternal LOAEL is 125 mg/kg bw/day based on increased incidence of ventral/genital staining of the fur and decreased maternal body-weight gains and food consumption. The maternal NOAEL is 50 mg/kg bw/day.

The number and percent of early intrauterine deaths were increased at 125 mg/kg/day (40 deaths; 14.8%) compared to controls (15 deaths; 6.3%), with a significantly higher ($p \leq 0.05$) proportion of dams affected at 125 mg/kg/day (14/21 dams) compared to controls (6/20 dams). Similarly, the number and percent of late intrauterine deaths were increased at 125 mg/kg/day (46 deaths; 18.7%) compared to controls (0 deaths; 0%), with a significantly higher ($p \leq 0.05$) proportion of dams affected at 125 mg/kg/day (14/21 dams) compared to controls (0/20 dams). The increases in early and late intrauterine deaths were reflected by an increased post-implantation loss at this dose (33.5% affecting 17/21 dams) compared to controls (6.3% affecting 6/20 dams).

Additionally at 125 mg/kg/day, mean gravid uterine weight, total litter weight, and live fetal body weights were decreased ($p \leq 0.01$) by 16-27%.

Incidences of the following skeletal variations, indicating skeletal retardation, were increased ($p \leq 0.05$) over concurrent controls and/or the provided historical control data: (i) in all treated groups - incompletely ossified unilateral and/or bilateral calcanea, partially ossified occipital, and not ossified odontoid; (ii) in the 50 and 125 mg/kg/day fetuses - unilateral and/or bilateral cervical rib and unilateral and/or bilateral extra (14) ribs; (iii) at 125 mg/kg/day - partially ossified parietals, increased fontanelle, partially ossified cervical arches between and including #3 and #6, partially ossified 1st sternebra, partially ossified 2nd sternebra, not ossified 5th sternebra, partially ossified, not ossified 6th sternebra, and partially ossified frontals. Mean scores for ossification of the *manus* were increased in all treated groups (2.66-3.13) compared to concurrent (2.42) and historical (1.88-2.59) controls. Similarly, mean scores for ossification of the *pes* were increased in all treated groups (3.06-3.63) compared to concurrent (2.72) and historical (2.53-3.05) controls. Aside from the variations listed above indicating skeletal retardation, there were no treatment-related external, visceral, or skeletal variations.

There were no treatment-related external, visceral, or skeletal malformations.

The developmental LOAEL is 50 mg/kg bw/day based on delayed ossification or non-ossification of the skeleton in the fetuses. The developmental NOAEL is 10 mg/kg bw/day.

This study is classified **unacceptable/guideline** and **does not satisfy** the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rats.

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 47521303), Flutriafol (95.1%; Batch # UPL Bx 1 (2001)) in corn oil was administered via daily oral gavage in a dose volume of 4 mL/kg to 22 presumed pregnant Wistar rats per dose group at doses of 0, 2, 5, 10, or 75 mg/kg bw/day from gestation days (GD) 6-20. On GD 21, all dams were euthanized; each dam's uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations and variations.

All dams survived until scheduled termination. There were no clinical signs of toxicity throughout the study, and no gross abnormalities were observed at necropsy. At 75 mg/kg/day, absolute maternal body-weight gains were decreased by 33% compared to controls during GD 6-9 and by 20% during GD 9-12. Body-weight gains for the overall (GD 6-21) treatment period were decreased by 8% compared to controls; when corrected for gravid uterine weight, body-weight gains were 28% lower than controls. When expressed as a percent of body weight on GD 6, body-weight gains were significantly decreased ($p \leq 0.01$) beginning the first day after dosing (GD 6-7) and continuing through GD 17. The decrease was most pronounced for GD 6-7 (decr 100%) and diminished to 13% lower than controls on GD 14. Although not statistically significant, relative body-weight gains at 75 mg/kg/day were also decreased (decr 11-12%) on GD 18 and 19. Additionally at this dose, mean body-weight gain for the overall (GD 6-20) treatment period was decreased by 9% ($p \leq 0.05$) compared to controls. Food consumption at this dose was decreased by 11-15% compared to controls throughout the treatment interval.

The maternal LOAEL is 75 mg/kg bw/day based on decreased body-weight gains and food

consumption. The maternal NOAEL is 10 mg/kg bw/day.

There were no abortions, premature deliveries, dead fetuses, or complete litter resorptions and no effects of treatment on the number of litters or sex ratio. The number of late resorptions at 75 mg/kg/day was higher than controls (21 treated *vs* 1 control), with the number of late resorptions per dam significantly increased ($p \leq 0.05$) at this dose (1.0/dam treated vs 0.0/dam controls). The number of early resorptions was also increased at 75 mg/kg/day (17 treated vs 12 controls), with the number of early resorptions per dam increased at this dose (0.8/dam treated vs 0.5/dam controls), although this increase was not significant. The increases in early and late resorptions, particularly late resorptions, resulted in a significantly decreased ($p \leq 0.05$) number of live fetuses/dam (11.7 treated vs 13.1 controls). Although numerically minor, there was a reduction in fetal weights at 75 mg/kg/day that was statistically significant and would correspond to the delay in development (non-ossified, incompletely ossified bones) at this dose level.

Treatment-related **malformations** were observed in the hyoid at 75 mg/kg/day compared to 0 concurrent and historical controls, including incidences of: misshapen arch (1% fetuses; 5% litters); absent body (1% fetuses; 5% litters); interrupted body (7% fetuses; 18% litters); and bent body (2% fetuses; 9% litters). Short intestine was noted in a single 75 mg/kg/day fetus and was not observed in the historical controls. Cleft palate was noted in a single fetus at 75 mg/kg/day. This uncommon malformation was also observed in a single fetus at 100 mg/kg/day in the supplementary range-finding study (MRID 47521302). It should also be noted that cleft palate occurred in a single historical control fetus. There were no other treatment-related external, visceral, or skeletal malformations.

Treatment-related **visceral variations** included misshapen nasopharynx lumen and displaced common carotid artery origin, which were observed at 75 mg/kg/day, but were not found in any concurrent or historical controls.

The following **skeletal variations** at 75 mg/kg/day were considered to be due to the test material because the fetal and litter incidences were dose-related and exceeded concurrent and historical controls: (i) additional ossification of the squamosal or zygomatic process of the maxilla; (ii) zygomatic arch fusion; (iii) blue-stained focus on the maxilla or mandible; (iv) accentuated curvature of the hyoid body; (v) long cervical rib; (vi) rudimentary cervical rib; (vii) caudal displacement of the pelvic girdle; (viii) bilateral radius and ulna bent; and (ix) cervical rib cartilage fused with thoracic rib 1 cartilage.

Fetal and litter incidences of the following treatment-related **skeletal retardations** were significantly increased ($p \leq 0.05$) at 75 mg/kg/day over concurrent controls and exceeded the range of historical controls: (i) incompletely ossified sternebra 6; (ii) unilateral left supernumerary rib; (iii) unilateral left rudimentary rib; (iv) unilateral right supernumerary rib; (v) unilateral right rudimentary rib; (vi) supernumerary unilateral left costal cartilage; (vii) supernumerary unilateral right costal cartilage. The incidence of non-ossification of the proximal phalanx of digit 2 on the left forelimb was significantly decreased ($p \leq 0.05$) at 75 mg/kg/day (0%) compared to concurrent controls and fell below the range of historical controls.

Additionally at 75 mg/kg/day, incidences of interrupted costal cartilage 10 were increased over concurrent and historical; however, only the fetal incidence was statistically significant ($p \leq 0.05$). Fetal and litter incidences of branched xiphoid cartilage were increased at 75 mg/kg/day over concurrent controls, with the fetal incidence attaining significance ($p \leq 0.05$) and exceeding the

historical controls; however, the litter incidence was not significant and fell within the range of historical controls. Similarly, an increased incidence of xiphoid cartilage with small hole was observed at 75 mg/kg/day compared to concurrent controls, with the fetal incidence attaining significance ($p \leq 0.05$); however, both the fetal and litter incidences fell within the range of historical controls. The incidence of cervical vertebral body 2 was lower at this dose compared to concurrent and historical controls, with the litter incidence attaining statistical significance ($p \leq 0.05$); however, incidences of this finding fell within the historical control range. Although the incidences of several of these findings were not significantly increased and/or fell within the range of historical controls, they were considered treatment-related because of their increase over concurrent controls and their corroboration of the generalized skeletal retardation.

Incidences of non-ossification of the proximal phalanges on toes 2-4 of both feet were significantly increased ($p \leq 0.05$) at 75 mg/kg/day compared to concurrent controls. Although the incidences of these findings fell within the range of historical controls, they were considered to be due to treatment due to the substantial and statistically significant increases over concurrent controls and the fact that this developmental delay is consistent with the other indications of skeletal retardation. Furthermore, the fact that these incidences fall within the range of historical controls is attributed to a single study (No. 857932).

In summarizing, administration of flutriafol to dams at 75 mg/kg/day results in teratogenicity (external, visceral and skeletal malformations), embryo-lethality, skeletal variations, a generalized delay in fetal development and fewer live fetuses.

The developmental LOAEL is 75 mg/kg bw/day based on: increased late resorptions; malformations (cleft palate and multiple hyoid malformations) and variations in the hyoid; variations in the maxilla/mandible, rudimentary and long cervical ribs, pelvic girdle, and radius/ulna; numerous skeletal retardations detailed above and corresponding decrease in fetal weights. The developmental NOAEL is 10 mg/kg bw/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700a; OECD 414) in rats.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 47090350), Flutriafol (PP450; 93%; Batch # P10) was administered daily in gelatin capsules to 24 presumed pregnant Dutch rabbits at doses of 0, 2.5, 7.5, or 15 mg/kg/day from gestation days (GD) 6-18. On GD 29, each surviving female was euthanized, and the uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations and variations.

At 7.5 mg/kg/day, one doe (#52) aborted part of its litter on GD 20. At 15 mg/kg/day, one doe (#70) was killed *in extremis* after observations that the animal had not been eating or drinking and that it had lost weight and was in poor condition. No other maternal deaths could be attributed to treatment. Loose feces on the cage floor and/or fur of the animals was observed in 2/15 rabbits at 7.5 mg/kg/day and 4/15 rabbits at 15 mg/kg/day. These findings were observed only once per female, except for one doe at 7.5 mg/kg/day for which the observation was made on 2 days and one doe at 15 mg/kg/day for which loose feces was noted on three days.

At 15 mg/kg/day, maternal body weight gains were decreased during the treatment interval (-79

g treated vs 48 g controls) and for the overall (GD 0-29) study, both when uncorrected for (149 g treated vs 230 g controls) and when corrected for (-158 g treated vs -55 g controls) gravid uterine weights. Additionally at this dose, maternal food consumption was increased by 24% ($p \leq 0.01$) over controls during the pre-treatment interval, but was decreased by 22% (not significant) during treatment.

In two of the females examined at 15 mg/kg/day, the stomach was found to contain a fur ball and was otherwise empty or contained little food. Only a single female at 7.5 mg/kg/day had little to no food in the stomach. Additionally at 15 mg/kg/day, one of the aforementioned does had dark pitted areas on the mucosal surface of the glandular portion of the stomach.

The maternal LOAEL is 15 mg/kg/day based on decreased corrected and uncorrected maternal body weight gains and food consumption.

The number of early intrauterine deaths was higher at 15 mg/kg/day than controls (36 deaths; 31.0%) compared to controls (11 deaths; 10.4%). Similarly, the number of late intrauterine deaths was increased at this dose (19 deaths; 16.4%) compared to controls (1 death; 1.0%). Complete litter resorptions were significantly higher ($p<=0.05$) at 15 mg/kg/day, occurring in 5/14 does compared to 0/15 controls. These findings resulted in a significantly increased ($p<=0.01$) post-implantation loss at 15 mg/kg/day (45.5% vs 13.1% controls); a decreased number of litters (9 vs 15); and a decreased total (61 vs 94) and mean (4.0 vs 6.5; $p<=0.05$) number of live fetuses.

There were no treatment-related effects on growth or development of the fetuses. Fetal body weights and litter weights of the treated groups were comparable to controls. Reduced/delayed ossification was observed in several bones in the skeleton (skull, vertebrae, and sternebrae) at an increased incidence over controls. However, these findings were minor in incidence and were not significantly different from the controls. Furthermore, mean scores for ossification of the *manus* and *pes* in all treated groups were comparable to controls.

There were no treatment-related external, visceral, or skeletal malformations or variations. Two fetuses, one at 7.5 mg/kg/day and another at 15 mg/kg/day, had multiple abnormalities; however, historical control data showed that similar findings were previously noted in individual fetuses (e.g., cleft palate, gastroschisis, malformed eyes, and shortened/flexed limbs with reduced number of digits). Furthermore, the findings in the fetus at 7.5 mg/kg/day were more severe than those in the 15 mg/kg/day fetus. All other findings were unrelated to dose, minor in incidence, and/or not significantly different from the controls.

The developmental LOAEL is 15 mg/kg/day based on decreased number of live fetuses, complete litter resorptions and increased post-implantation loss. The developmental NOAEL is 7.5 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits.

A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a two-generation reproduction toxicity study (MRID 47090351), Flutriafol (93%; Batch # P10) was administered in the diet to 15 male and 30 female Wistar rats/sex/dose group at dietary levels of 0, 60, 240, or 1000 ppm (0, 4.8, 20.6 and 88.7 mg/kg bw/day in P males; and, 0, 5.5, 21.9 and 103 mg/kg bw/day in P females) The P generation animals were fed the test diets for 12 weeks prior to mating to produce the F1a litters. After weaning of the F1a litter, the females were mated with a different male to produce the F1b litters. On post-natal day (PND) 36, offspring from the F1b litters were selected to be parents and were fed the same test diet concentration as their dam for 11 weeks prior to mating to produce the F2a litters. This procedure continued through weaning of the F2b litters which was produced by mating of the F1b.

There were no treatment-related deaths or clinical signs of toxicity.

Treatment-related effects on body-weight gain, food consumption, and food utilization during the pre-mating period were observed at 1000 ppm.

Body-weight gains were decreased ($p \leq 0.05$, unless otherwise noted) at 1000 ppm compared to controls: throughout the pre-mating period in the P males (decr. 6-8%); beginning at Week 7 in the P females (decr. 4-6%, not significant [NS] at Week 8); and throughout pre-mating in the F1 females (decr. 6-18%; NS at Week 6).

Food consumption was decreased ($p \leq 0.05$) at 1000 ppm compared to controls: generally throughout pre-mating in the P males (decr. 4-7%), resulting in a decrease in total food consumption (Weeks 1-12) of 2% ($p \leq 0.01$) compared to controls; beginning at Week 6 in the P females (decr. 6-8%), resulting in a decrease of 5% ($p \leq 0.01$) in total food consumption; and at Week 8 in the F1 females (decr. 6%; $p \leq 0.01$).

Food utilization was increased by 3% ($p \leq 0.01$) compared to controls in the 1000 ppm P males for Weeks 1-4. Food utilization was increased by 10% ($p \leq 0.05$) over controls in the F1 females at this dose for Weeks 1-4, resulting in an increase of 8% ($p \leq 0.01$) for the overall (Weeks 1-11) pre-mating period.

Throughout gestation, cumulative body-weight gains were decreased by 3-25% at 1000 ppm in the P dams during both litters and in the F1 dams during the F2b litter. With the exception of the P females on GD 8 and 22 during the F1a litter and the F1 females on GD 22 during the F2b litter, these decreases were significantly ($p \leq 0.05$) different from controls.

Absolute and adjusted (for body weight) liver weights were increased ($p \leq 0.01$) by 11-29% over controls in both sexes in both generations, with the exception of the absolute liver weight in the P females, which was increased by 6% over controls (NS).

Treatment-related microscopic findings were found in the liver. Centrilobular hypertrophy was observed in 1000 ppm males in the P generation (2/15 treated vs. 0/15 controls) and F1 generation (4/15 treated vs. 0/15 controls). Increased incidences of fatty change in the liver were observed at this dose in the P generation males (8/15 treated vs. 0/15 controls) and females (5/30

treated vs. 1/30 controls) and in the F1 generation males (13/15 treated vs. 0/15 controls) and females (3/30 treated vs. 0/30 controls). Fatty change was also observed in the 240 ppm F1 males (5/15 treated vs. 0/15 controls).

The LOAEL for parental toxicity is 1000 ppm (88.7/103 mg/kg bw/day in males/females) based on decreased body-weight gains and food consumption and on effects on the liver (increased liver weights, centrilobular hypertrophy, and fatty change). The NOAEL is 240 ppm (20.6 mg/kg bw/day in P males and 21.9 mg/kg bw/day in P females).

Although no data were provided, it was stated that the offspring generally remained in good clinical condition and that there were no clinical abnormalities which could be related to treatment. There were no effects of treatment on the offspring survival indices (percent pups surviving to PND 22 and proportion of litters with all pups surviving to PND 22) or cumulative pup body-weight gains throughout the post-natal period. At necropsy, no macroscopic findings could be attributed to treatment.

At 1000 ppm, litter size was decreased ($p \leq 0.05$) throughout the post-natal period in the F1b litter (decr. 17-18%) and in the F2a litter (decr. 22-23%). The percent of pups born alive was decreased ($p \leq 0.05$) in the F2a litter (94.9% treated vs. 100% controls) and F2b litter (90.1% treated vs. 99.3% controls). The proportion of litters with all pups born alive was decreased at this dose in the F2a litter (15/20 treated vs. 18/18 controls) and F2b litter (19/29 treated vs. 24/26 controls). In the liver, fatty change was observed at 1000 ppm in the F1b male pups (1/7 treated vs. 0/6 controls) and F1b female pups (1/6 treated vs. 0/8 controls). Fine vacuolar hepatocyte vacuolation/fatty change was observed in the F2b males (5/10 treated vs. 0/10 controls) and F2b females (1/10 treated vs. 0/10 controls).

The LOAEL for offspring toxicity is 1000 ppm (88.7/103 mg/kg bw/day in males/females) based on decreased live birth index and litter size and on effects on the liver (fatty change/vacuolation). The NOAEL is 240 ppm (approximately equivalent to 20.6 mg/kg bw/day in males and 21.9 mg/kg b w/day in females).

There was no apparent effect of treatment on estrous cycle duration or periodicity in the P generation. There were no effects of treatment on precoital interval, gestation duration, or fertility in either litter in either generation.

The LOAEL for reproductive toxicity was not observed. The NOAEL is 1000 ppm (approximately equivalent to 88.7/103 mg/kg bw/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

A.3.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

In a combined chronic toxicity/carcinogenicity study (MRID 47090352), 52 Alpk:AP rats/sex/dose were exposed to flutriafol (93% a.i.; Batch No.: P10) for up to 24 months in the diet at concentrations of 0, 20, 200, or 2000 ppm (calculated to be, 0, 1.02, 10.0, and 102 mg/kg bw/day in males; and 0, 1.27, 12.2 and 122 mg/kg bw/day in females). Additionally, 12

rats/sex/dose were treated similarly for up to 12 months.

No treatment-related effects were observed on mortality, ophthalmology, clinical chemistry, or urinalysis.

Grossly, small discolored foci were commonly observed after 2 years of treatment. After 1 year of treatment, an increased incidence of fatty change in the liver was observed in the 200 and 2000 ppm males (21-93% of treated rats vs 7% controls). The severity was minimal in the controls and 200 ppm males, but was minimal to marked in the 2000 ppm males. After 2 years of treatment of the 200 and 2000 ppm males, increased incidences of minimal to severe hepatic fatty change (54-96% treated vs 24% controls) and clear cell foci of hepatocytes (40-50% treated vs 18% controls) were observed.

At 2000 ppm, systemic toxicity was noted in both sexes as follows. More rats appeared thin and fewer rats had distended abdomens. Final body weights were decreased by 12-22%, and cumulative body-weight gains were decreased by 12-48% throughout the study. Weekly food consumption was frequently decreased by 4-24% throughout treatment, and total food consumption was decreased by 8-12% for the Weeks 1-13 interval. Food utilization (g food/g growth) was increased by 8-11% for the Weeks 1-4 interval, and by 7% (each sex) for the Weeks 1-12 interval.

A slight treatment-related anemia was noted in the 2000 ppm group as indicated by the following decreases ($p \leq 0.05$) in hematological parameters: (i) hemoglobin in males (↓4-7%) during Weeks 4-65 and females (↓4-9%) during Weeks 13-52, 78, and 92; (ii) hematocrit in males (↓3-8%) during Weeks 26-65 and females (↓5-11%) during Weeks 13-52, 78, and 104; (iii) mean cell volume in males (↓3-8%) during Weeks 4-104 and females (↓2-10%) during Weeks 4-104; and (iv) mean cell hemoglobin in males (↓4-7%) during Weeks 4, 26, 39, and 78-104 and females (↓4-10%) during Weeks 4-52 and 78-104. The total iron binding capacity of the 2000 ppm females was increased ($p \leq 0.01$) by 40%. Increased ($p \leq 0.05$) lymphocytes were observed in the 2000 ppm females (↑22-61%) during Weeks 26-78 and 104, and increased ($p \leq 0.05$) total leukocytes were noted at Weeks 26, 39, and 78 (↑20-38%). The hematological changes were not considered to be an adverse effect due to the minor decreases in magnitude without corroborating clinical signs.

At 2000 ppm, the following toxicologically significant differences ($p \leq 0.05$) were observed: (i) increased plasma cholesterol in the females throughout the study (↑24-49%; NS at Week 91); (ii) decreased plasma triglycerides in the males during Weeks 4-65 (↓40-68%); (iii) decreased alkaline phosphatase in the males during Weeks 13-91 (↓12-33%); (iv) increased plasma total protein in the females throughout treatment (↑4-9%); and (v) increased plasma alanine transaminase during Weeks 4 and 13 (↑54-82%).

At 2000 ppm, hepatoxicity was noted in both sexes. In both sexes, increased liver weights, both absolute and adjusted for body weight, were observed after 1 year of treatment (incr 11-37%) and after 2 years (incr 27-34%, except similar to control for absolute liver weight of the females). There was hepatic enlargement, often coupled with the presence of numerous discolored foci, commonly observed in both sexes. These liver findings were observed after 2 years of treatment, but not after 1 year of treatment. After 2 years of treatment, the following histological hepatic lesions were increased in incidence in the females: (i) minimal to severe fatty change (65% treated vs 23% controls); (ii) bile duct proliferation/ cholangiolarfibrosis (67% treated vs 44%

controls); (iii) hemosiderin accumulation in Kupffer cells (55% treated vs 0% controls); and (iv) centrilobular hypertrophy (8% treated vs 0% controls). Hepatic centrilobular hypertrophy was increased in incidence at the interim sacrifice in males (71%) and females (31%), but only minor increases were noted at terminal sacrifice in both sexes (6-8%) with 0% in the controls. An increased incidence of foci of cortical macrophages in adrenal glands was observed in the 2000 ppm females (80% treated vs 25% controls); however, there was no corroborating evidence of toxicity in the adrenal gland, and this lesion alone was not considered adverse.

The LOAEL is 2000 ppm (102/122mg/kg bw/day in males/females), based on adverse liver effects (increased liver weights, fatty change, bile duct proliferation/cholangiolarfibrosis, hemosiderin accumulation in Kupffer cells and centrilobular hypertrophy), and clinical chemistry findings. The NOAEL is 200 ppm (10.0/12.2 mg/kg bw/day in males/females).

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body-weight gain and food consumption, increased food utilization, and hepatotoxicity observed in both sexes.

This study is classified as **Acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

870.4100b Chronic Toxicity – Dog

In a chronic toxicity study in dogs (MRID 47090353), flutriafol (PP450; 93.0% a.i.; batch # P10) was administered to four beagle dogs/sex/dose group daily by capsule for at least 52 weeks at doses of 0, 1, 5, or 20 mg/kg bw/day.

No adverse, treatment-related effects were observed on mortality, clinical signs of toxicity, food consumption, ophthalmoscopic examinations, or gross pathology.

One 20 mg/kg/day female was observed to be subdued and not eating during Week 15. This dog was dehydrated and thin, had pale mucus membranes, loud intestinal sounds and a tense abdomen, with marked reduction in muscle mass. Mucus containing blood was present in the feces, and vomit was present on the pen floor on three days. This animal was killed for humane reasons during Week 16. In view of the limited toxicity noted in the other dogs receiving 20 mg/kg/day, it was unclear if the poor condition of this dog was due to administration of the test compound.

The liver was a target organ. At 20 mg/kg/day, liver weights were increased ($p \leq 0.01$) by 27-39% in both sexes. The following treatment-related alterations in clinical chemistry parameters were observed: (i) alkaline phosphatase was increased ($p \leq 0.01$, except not significant [NS] for Week 13 males) by 60-268% in both sexes during Weeks 4, 13, 26, and 52, and the increases became greater in magnitude with time of exposure; (ii) albumin was decreased ($p \leq 0.05$) by 15-19% during Weeks 4, 13, 26, and 52 in the males, and by 9-10% during Weeks 13 and 26 in the females; and (iii) triglycerides were increased ($p \leq 0.05$) by 31% during Week 52 in the males, and by 62-71% during Weeks 4 and 13 in the females. Additionally, minimal to slight increased centrilobular hepatocyte lipid in the liver was noted in 3/4 females vs. 0/4 controls.

Body weight losses ($p \leq 0.05$) of 0.02-0.17 kg were observed in the females during Weeks 1 and 2. These animals did not recover over the course of the study, and demonstrated decreased (not

significant [NS]) cumulative body-weight gains for the study period (Weeks 0-52; decr. 28%). Adrenal weights were increased ($p \leq 0.01$) by 38% in the females, and increased cortical vacuolation of the zona fasciculata was observed in the adrenal in 4/4 males (slight severity) and 4/4 females (minimal to slight severity) vs. 0/4 controls of both sexes. Additionally in the males, during Weeks 26 and 52, hemoglobin was decreased ($p \leq 0.05$) by 7-9%, hematocrit was decreased ($p \leq 0.05$ for Week 52; NS for Week 26) by 8-11%, and red blood cell counts were decreased (NS). Marked liver sinusoidal cell hemosiderin pigmentation was observed in 4/4 males and 4/4 females vs. minimal to moderate in 4/4 controls of both sexes, and marked hemosiderin pigmentation in the spleen was noted in 4/4 males and 4/4 females vs. minimal to moderate in 4/4 controls of both sexes.

At 5 mg/kg/day, a minimal severity of cortical vacuolation of the zona fasciculata was present in one female and one male out of a total of 8 animals. RAB1 toxicologists concluded that this minimal effect in the adrenal gland was not an adverse effect.

The LOAEL is 20 mg/kg/day, based on: adverse liver findings (increased liver weights, increased centrilobular hepatocyte lipid in the liver, and increases in alkaline phosphatase, albumin and triglycerides), increased adrenal cortical vacuolation of the zona fasciculata, and marked hemosiderin pigmentation in the liver and spleen in both sexes; mild anemia (characterized by decreased hemoglobin, hematocrit, and red blood cell count) in the males; and initial body weight losses, decreased cumulative body-weight gains, and increased adrenal weights in the females. The NOAEL is 5 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4100) for a chronic oral toxicity study in dogs.

A.3.5 Carcinogenicity

870.4200a Carcinogenicity Study – Rat

(see A.3.4 870.4100a Chronic Toxicity- rat)

870.4200b Carcinogenicity (feeding) - Mouse

In a carcinogenicity study (MRID 47090354), Flutriafol (93% a.i.; Batch No. P10) was administered in the diet to C57BL/10JfCD-1/Alpk mice (50/sex/dose) for up to 2 years at doses of 0 (two control groups), 10, 50, or 200 ppm (calculated to be 0, 1.1, 5.9, and 24 mg/kg bw/day in males; and 0, 1.4, 7.4 and 31 mg/kg bw/day in females).

No adverse treatment-related effects were observed on mortality or food consumption.

At 200 ppm, increased incidences were observed in discharge from the eye (both sexes) and thickened eyelids (females). Body weights were decreased ($p \leq 0.05$) generally throughout the study in both sexes (decr. 2-8%). Overall (Weeks 1-104) body-weight gains were decreased in the males (decr. 18%; $p \leq 0.01$) and females (decr. 8%; not statistically significant [NS]); and decreased ($p \leq 0.01$) food efficiency was observed in the males during Weeks 1-4 (decr. 38%) and 1-12 (decr. 21%). Additionally, increased ($p \leq 0.05$) platelet (incr 42%), white blood cell (incr 62%), neutrophil (incr. 81%), and lymphocyte (incr 58%) counts were noted in the males. Hepatotoxicity was also noted. Increased ($p < 0.01$) liver weights (absolute and adjusted for body

weight) were observed in males (incr. 32-37%) and females (incr. 17-26%). Furthermore, increased incidences (# affected/50 in treated vs controls) of minimal to marked hepatic centrilobular fatty change were noted in the males (23 vs. 1) and females (17 vs. 0); and minimal to moderate hepatic centrilobular hypertrophy were noted in the males (14 vs 0-1) and females (3 vs 0).

At 50 ppm, a slight effect was observed on body weights and body-weight gains in males. Body weights were decreased by 5% ($p \leq 0.05$) on Week 104, and overall (Weeks 1-104) body-weight gains were decreased by 8% (NS). Furthermore, a treatment-related increased incidence of hepatic centrilobular fatty change was noted in 6/50 males (1 minimal, 4 slight, and 1 marked severity).

The LOAEL is 200 ppm (24/31 mg/kg bw/day in males/females), based on hepatotoxicity (increased fatty change) in both sexes. The NOAEL is 50 ppm (5.9/7.4 mg/kg bw/day in males/females).

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. There was an apparent increase in the incidence of generalized composite lymphomas in the 200 ppm female decedents (100% treated vs 62% controls). Although this finding was statistically significant ($p \leq 0.05$), the difference was no longer evident when all animals were considered (92% treated vs 81-91% controls). Furthermore, the effect was not clearly dose-dependent. Dosing was considered adequate based on decreases in body weights and body-weight gain in both sexes, decreased food efficiency in males, hematological findings in males, and hepatoxicity in both sexes.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

A.3.6 Mutagenicity

Gene Mutation	
870.5100, *In vitro* Bacterial Gene Mutation *(Salmonella typhimurium)*/ mammalian activation gene mutation assay MRID 47090401 Acceptable/guideline	0, 1.6, 8, 40, 200, 1000, or 5000 µg/plate (Trial 1) or 0, 8, 40, 200, 1000, 2500, or 5000 µg/plate (Trial 2); Both trials were performed w/wo S9-activation. There were no marked increases in the mean number of revertants/plate in any strain. There was no evidence of induced mutant colonies over background.

870.5300, *In Vitro* Gene Mutation assay in mouse lymphoma cells MRID 47090402 Acceptable/guideline	0, 10, 33, 100, 333, or 1000 µg/mL (+S9, Trial 1); 0, 150, 300, 450, 600, or 750 µg/mL (-S9, Trial 1); 0, 150, 300, 450, 600, 750, 900, 1050, or 1200 µg/mL (+S9, Trial 2); or 0, 200, 300, 400, 500, 600, 700, or 800 µg/mL (-S9, Trial 2). There was a dose-related increase in mutant frequency (7.0-9.0x10^{-5} treated vs. 3.0x10^{-5} controls) and absolute mutant numbers (70-148 colonies/plate vs. 63 controls) at 100 µg/mL and above in Trial 1 and a marked increase in mutant frequency at 750 µg/mL (6.5x10^{-5} treated vs. 1.2x10^{-5} controls) in Trial 2 attributable to severe cytoxicity (2% relative survival). However, the increases in mutant frequency did not achieve the threshold value for a positive response (>10x10^{-5}) in either trial and there was no marked increase in absolute mutant numbers at 750 µg/mL in Trial 2. In the absence of S9, there were no marked increases in mutant frequency or absolute mutant numbers compared to controls in either trial. There was no convincing evidence of induced mutant colonies over background in the presence or absence of S9-activation.

Cytogenetics	
870.5375, *In vitro* Mammalian Cytogenetics (Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes) MRID 47090403 Acceptable/guideline	No significant increases in the numbers of cells with aberrations (excluding gaps) were observed in either donor in the presence or absence of S9. There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation.
870.5385, *In vivo* Mammalian Cytogenetics – [Bone Marrow Chromosomal Aberration Test MRID 47090404 Acceptable/guideline	0, 15, 70, or 150 mg/kg. There was no evidence of chromosome aberration induced over background.
870.5395, *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in Mice MRID47090405 Acceptable/guideline	0, 93.8, or 150 mg/kg. Decreased ($p<0.01$) polychromatic erythrocyte to normochromatic erythrocyte ratios (PCE:NCE) were observed in both doses at all time points, indicating that the test material was toxic to the bone marrow. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.

Other Genotoxicity	
870.5450, Dominant Lethal Assay – Mice MRID 47090406 Acceptable/guideline	0, 25, 50, or 100 mg/kg/day (total doses of 0, 125, 250, or 500 mg/kg). Mortality (3/15 males) was noted at 100 mg/kg/day during dosing. Slight decreases ($p<0.05$) in body weight were observed at 50 mg/kg/day and above during dosing. There were no treatment-related effects on fertility, mean number of implantations, or the number of early or late deaths. There was no time-related positive response of increased pre- or post-implantation loss compared to controls.
870.5550, Unscheduled DNA Synthesis in Primary Rat Hepatocytes/Mammalian Cell MRID 47090407 (2003) Acceptable/guideline	0, 250, 500, or 1000 mg/kg. The net nuclear grain (NNG) counts in the treated animals (–3.42 to –2.64) were well below the threshold of ≥ 5 NNG needed for a positive response, and no increase in the mean percent of cells in repair was observed. There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.

A.3.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery - Rat

In an acute neurotoxicity study (MRID 47090408), Flutriafol (95.1% a.i.; Lot # UPL Bx 1 [2001]) was administered once via gavage (10 mL/kg) to 10 Sprague-Dawley rats/sex/group at

dose levels of 0, 125, 250, or 750 mg/kg. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed on 10 rats/sex/group at pre-dosing and Days 1 (approximately 8 hours post-dosing; estimated time of peak effect), 8, and 15. At study termination, 5 rats/sex/group were anesthetized and perfused *in situ* for neuropathological examination. The tissues from the perfused animals in the control and 750 mg/kg groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Acceptable positive control data were provided.

No compound-related effects were observed in brain weights or gross or neuropathology.

At 125 mg/kg, males exhibited a dose-dependent body weight loss of -4.2% on Days 1-2. At 250 mg/kg and above, dose-dependent losses (-4.2-28.5 g) ($p<0.01$) in body weight were observed in both sexes on Days 1-2. On Days 2-3, body-weight gains were increased (52-74%) ($p<0.05$) in both sexes at 250 mg/kg but remained decreased in both sexes at 750 mg/kg. The increase in the 250 mg/kg females was sufficient to compensate for the initial body weight loss and allowed the body weights in this group to remain similar to controls for the remainder of the study. Despite the increase at 250 mg/kg, the body-weight gain remained decreased in the 250 mg/kg males during the interval, 1-3 days (-76%). At 750 mg/kg, overall (Days 1-16) body-weight gain was decreased in the males (-20%) ($p<0.01$) and females (-17%) (NS). In the males, dose-dependent decreases ($p<0.01$) were noted in both absolute and relative food consumption on Days 1-2 in the 250 mg/kg group (64% and 63%, respectively) and the 750 mg/kg group (89% and 88%, respectively). This initial decrease resulted in a continued reduction in both absolute and relative food consumption in males on Days 1-3. In the 750 mg/kg males, overall (Days 1-16) absolute food consumption was decreased (-15%) ($p<0.01$) compared to controls while no statistically significant decrease in relative food consumption was observed. In the 750 mg/kg females, no statistically significant decreases in absolute or relative food consumption were observed during the remainder of the study or in the overall (Days 1-16) values.

Additionally at 750 mg/kg, 4/10 males and 2/10 females were sacrificed in moribund condition on Days 2 or 3. Increases ($p<0.01$) were noted in the incidence of the following clinical signs in the males (unless otherwise stated): dehydration (both sexes), chromorhinorrhea, urine-stained abdominal fur (both sexes), ungroomed coat (both sexes), decreased motor activity, chromodacryorrhea, ptosis, lost righting reflex, scant feces, and red or tan perioral substance. The following additional clinical signs of toxicity were noted in the animals sacrificed in a moribund condition: males (prostration, limp muscle tone, muscle flaccidity, hypothermia, hunched posture, and labored breathing) and females (ptosis, prostration, piloerection, bradypnea, decreased motor activity, impaired righting reflex, lost righting reflex, limp muscle tone, scant feces, and hypothermia).

At 125 mg/kg, effects were limited to minor decreases ($p<0.01$) in body-weight gain and absolute and relative food consumption in the males.

At 750 mg/kg, increased ($p<0.01$) incidence (# affected/10 vs. 0 controls) of the following neurological effects were noted at 8 hours post-dosing during the FOB: (i) hunched posture in 6 males and 4 females and (ii) slight ataxia in 3 males. All findings were resolved by Day 8. No statistically significant differences were observed on either the interval or total session motor activity (number of movements or time spent in movement). However, at 8 hours post-dosing, total session number of movements and time spent in movement were slightly decreased in both sexes. These parameters remained decreased in the males on Day 8. These changes in motor

activity were observed at a dose that resulted in moribundity and are considered related indirectly to the overall toxicity of the test material. No treatment-related microscopic lesions were observed.

The LOAEL is 750 mg/kg, based on decreased body weight, body-weight gain, absolute and relative food consumption, and clinical signs of toxicity, indicative of a moribund condition, in both sexes: dehydration, urine-stained abdominal fur, ungroomed coat, ptosis, decreased motor activity, prostration, limp muscle tone, muscle flaccidity, hypothermia, hunched posture, impaired or lost righting reflex, scant feces; in males: red or tan perioral substance, chromodacryorrhea, chromorhinorrhea and labored breathing, and in females: piloerection and bradypnea, and signs of neurotoxicity: hunched posture in females and ataxia in males. The NOAEL is 250 mg/kg.

The study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.6200a) for a neurotoxicity screening battery in rats.

870.6200 Subchronic Neurotoxicity - Rat

In a subchronic neurotoxicity study (MRID 47090410), Flutriafol (95.1% a.i.; Lot # UPL Bx 1 [2001]) was administered in the diet to 10 Sprague-Dawley rats/sex/group at dose levels of 0, 500, 1500, or 3000 ppm (equivalent to 0/0, 28.9/32.6, 84.3/97.6, and 172.1/185.0 mg/kg/day [M/F], respectively) for 92 days. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) were performed in 10 rats/sex/group at pre-dosing and Weeks 2, 4, 8, and 13. At study termination, 5 rats/sex/group were anesthetized and perfused *in situ* for neuropathological examination. The tissues from the perfused animals in the control and 3000 ppm groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Acceptable positive control data were provided.

No compound-related effects were observed in mortality, clinical signs of toxicity, ocular effects, motor activity, brain weights, or gross or neuropathology.

At 1500 ppm, body-weight gains were decreased ($p \leq 0.05$) in the males by 28% compared to controls during the first week of dosing and overall (Days 1-92) body-weight gain was decreased ($p \leq 0.05$) by 19% in the females. Likewise, absolute and relative food consumption were decreased ($p \leq 0.01$) by 15-16% in both sexes during Week 1.

At 3000 ppm, body weights were decreased throughout the study in the males (decr. 5-14%) and females (decr 5-10%) and attained statistical significance ($p \leq 0.05$) at Days 8 and 57 through 92 in the males and Days 50, 64, and 85 through 92 in the females. During the first week of dosing, body-weight gains were decreased ($p \leq 0.05$) by 108% in both sexes at this dose compared to controls. During Week 2, body-weight gain was increased ($p \leq 0.01$) by 36% in the males. Overall (Days 1-92) body-weight gain was decreased ($p \leq 0.05$) by 23-34% in the males and females compared to controls. Similarly, absolute and relative food consumption were decreased ($p \leq 0.01$) by 35-40% in both sexes during the first week of dosing. Additionally in the females, absolute food consumption was decreased ($p \leq 0.05$) by 9-14% at most intervals throughout the exposure period. Overall absolute food consumption was decreased ($p \leq 0.01$) by 10-13% in both sexes. During Week 2, relative food consumption was increased ($p \leq 0.01$) by 10% in the males. In the females, relative food consumption was slightly lower throughout the rest of the exposure period, but only attained statistical significance (decr 8%; $p \leq 0.01$) on Days 29-36. Overall

relative food consumption was only slightly decreased (decr 5%; not statistically significant) in the females.

Additionally at 3000 ppm, hindlimb grip strength was decreased ($p \leq 0.05$) in the males by 17% compared to controls during Week 2. The decreased hindlimb grip strength was considered to be a treatment-related neurotoxic effect.

No treatment-related effects were observed at 500 ppm in either sex.

The LOAEL was 3000 ppm (equivalent to 172.1/185.0 mg/kg/day [M/F]) based on decreased body-weight gain, and absolute and relative food consumption and decreased hindlimb grip strength. The NOAEL is 1500 ppm (equivalent to 84.3/97.6 mg/kg/day [M/F]).

The study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.6200b) for a subchronic neurotoxicity study in rats.

A.3.8 Special

870.7485 Metabolism – Rat

In rat metabolism studies (MRIDs 47090412, 47090413, and 47090414), ^{14}C-flutriafol (>97% radiochemical purity) in polyethylene glycol 600 was administered to rats as a single oral gavage dose at 5 or 250 mg/kg body weight. Group sizes were 1 rat/sex in a preliminary study at 5 mg/kg, 2 rats/sex/dose in bile duct-cannulation studies, one group of 6 females at 250 mg/kg, and 4-5 rats/sex/dose in other dose groups. One group of 4 rats/sex received 14 consecutive daily doses at 5 mg/kg/day. ^{14}C-carbinol-flutriafol was administered to all groups, except one group of 2 rats/sex was treated with 5 mg/kg ^{14}C-triazole-flutriafol. Excreta (urine, feces, and bile [in some groups]) were collected, and analyzed for radioactivity concentration. Additionally, pools of selected excreta were analyzed to identify and quantify metabolites. Animals were sacrificed at 48 hours in the preliminary experiment and at 72 or 168 hours post-dose or post final dose in the other studies. Tissues were collected and analyzed for radioactivity concentration.

More than 78% of the administered dose was recovered in the bile and urine of the single 5 mg/kg (both radiolabels) and 250 mg/kg dose groups. Absorption was generally similar between sexes, radiolabels, and between single and multiple dose regimes. Comparing absorption in 5 mg/kg groups to the 250 mg/kg groups, absorption remains extensive; however, a longer time is required for absorption to complete.

Total recoveries at 168 hours post-dose were 97-99% of the administered single dose and 115-125% daily dose in the multiple dose study. The administered dose was mostly eliminated within 48 hours at 5 mg/kg (86-97% of the single dose or 104% daily dose of the multiple dose groups) and at 250 mg/kg (68-85% dose, except bile duct-cannulated females which was 38% dose).

Only 0.04-0.05% of the dose was found in the expired carbon dioxide in a preliminary study. In the bile duct-cannulation study, most of the radioactivity was excreted in the bile (47-79% of the dose). In the single dose 5 mg/kg group (not bile duct-cannulated), similar amounts of radioactivity were excreted in the feces as in the urine, but only approximately half as much was

excreted in the feces as in the urine at 250 mg/kg. Slightly more radioactivity was found in the urine of the multiple dosed animals compared to the single dosed animals. The excretion profile was generally similar between the sexes, and was also similar following 1, 5, 10, and 14 doses.

Tissue distribution was examined in animals sacrificed 168 hours post-dose. In the blood, radioactivity partitioned into the red blood cells. In animals receiving multiple daily 5 mg/kg doses, concentrations of radioactivity were higher in the blood cells than plasma of males (218-fold) and females (129-fold). Excluding blood cells and GI tract measurements, the highest concentrations were found in whole blood in males (190 ng equivalents flutriafol/g tissue in the single 5 mg/kg dose group, 8040 ng equiv/g in the 250 mg/kg dose group, and 1450 ng equiv/g in the multiple 5 mg/kg/day dose group) and in females (140 ng equivalents flutriafol/g tissue in the single 5 mg/kg dose group, 6740 ng equiv/g in the 250 mg/kg dose group, and 519 ng equiv/g in the multiple 5 mg/kg/day dose group). In both sexes and all groups, concentrations of radioactivity were relatively high in both liver and kidneys. Other organs with high concentrations in one or more groups included the adrenal glands, spleen, and pituitary. The distribution profiles were generally similar between species, dose level, and single vs multiple dose regime. A 50-fold increase in dose resulted in an approximately 42-48-fold increase in radioactivity concentrations in the whole blood; thus, the concentrations were roughly proportional to the dose.

The total amount of radioactivity isolated in the tissues and carcass was miniscule: <1% of the administered dose (single dose groups) or 3% of the daily administered dose (multiple dose group). Also, the amount of the dose remaining in the body (GI tract and contents, tissues, and remaining carcass) after 168 hours was <1.1% of the administered dose regardless of sex, radiolabel position, or dose. For these reasons, bioaccumulation in all dose groups was considered unlikely.

The parent was isolated in only trace amounts in the urine and feces (<0.5% of the administered dose) and more than 19 metabolites were isolated, indicating extensive metabolism of flutriafol. In general, metabolism profiles were similar between sexes. The metabolism profile in urine was similar between the 250 mg/kg dose group and the multiple 5 mg/kg dose group, but the metabolism profiles in feces resulted in the isolation of greater amounts of identified compounds in the high dose group. Summarizing the Sponsor's stated results in MRID 47090413 (data not provided); the metabolic profiles were similar regardless of the matrix (feces, urine, or bile), the dose, the sex, or the radiolabel.

The primary site for metabolism was the 2-fluorophenyl ring. The initial metabolic step was probably epoxidation followed by either rearrangement to form the dihydrodiol isomers or to form hydroxy or dihydroxy metabolites. The hydroxyl groups on these primary metabolites may then be either conjugated with glucuronic acid or methylated. A second, minor route for metabolism of flutriafol was via the removal of the triazole ring to form 1-(2 fluorophenyl)-1-(4-fluorophenyl)-ethandiol, which is then conjugated with glucuronic acid.

This metabolism study in the rat is classified **acceptable/guideline** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

870.7600 Dermal Absorption - Rat

In a dermal penetration study (MRID 47090415), ^{14}C-carbinol-flutriafol (98-99% radiochemical

purity as applied; Batch No. Rad164) was applied to the skin (10 cm^2) of Sprague Dawley rats (4 males for each time point at each dose level). Nominal doses of 0.02, 0.2 or 2 mg/cm^2 skin were tested (10 $\mu l/cm^2$ skin), and actual doses were 0.0208, 0.201, and 2.154 mg/cm^2 skin. The exposure durations were 0.5, 1, 2, 4, 10, and 24 h, and the animals were terminated at the end of the exposure period. An additional group was exposed for 10 h and maintained for another 158 h in the metabolism unit prior to termination.

Recovery of the applied dose (mass balance) was 96-103%. The majority of the dose was not absorbed (sum of soap and water wash of the application site with the dose site appliance wash; generally 75-97% of the applied dose), with the greatest amount of radioactivity being recovered from the soap wash of the application site (generally 51-87% of the applied dose). Dermal absorption (based on the sum of residues in urine, feces, cage wash, blood, and carcass) ranging up to 15.8% of the applied dose was noted. Absorption was minimal with only 4 h of exposure (<1.5% of the applied dose), and was saturated in the high dose (maximum absorption of only 3.7% dose). Absorbable radioactivity (radioactivity in the skin at the application site and the adjacent skin) was minimal (<0.75% of the applied dose) in groups that were exposed for 10 h and evaluated for an additional 158 h post-exposure. Thus, the data suggests that almost all of the dose isolated in the skin will be absorbed. Considering the sum of absorbable and absorbed doses, 4-37% of the applied dose was recovered in the treatment groups (mean of 11% and median of 9%). Absorption rate constants were calculated as 0.236, 0.190, and 0.072 h^{-1} for the 2, 20, and 200 $\mu g/cm^2$ dose groups, respectively; thus, absorption mechanisms were saturated at the high dose. The elimination half-lives were calculated to be 31, 30, and 37 h for the 2, 20, and 200 $\mu g/cm^2$ dose groups, respectively.

As almost all of the absorbable dose (radioactivity in the skin at the application site and the adjacent skin) will be absorbed, the most conservative estimation of absorption would consider both the absorbed dose and the absorbable dose. In this study, a maximum of 36.56% of the applied dose was noted as absorbed/absorbable (observed after 24 h exposure to 2 $\mu g/cm^2$). This value is most conservative. However, it is likely that any area exposed to the chemical will be washed within 10 h. The applied dose that is absorbed/absorbable following a 10 h exposure is 16.54%, 21.31% and 11.39% , respectively, at 2, 20 and 200 $\mu g/cm^2$.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.7600; OECD none) for a dermal penetration study in rats.

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Appendix B. Metabolism Assessment

Plant Metabolism Studies: The petitioner submitted apple, sugar beet, rapeseed, and wheat/barley (foliar and seed treatment) metabolism studies conducted with [triazole-3,5-^{14}C]flutriafol and [carbinol-^{14}C]flutriafol. HED notes that the wheat/barley metabolism studies were deemed unacceptable due to numerous deficiencies but are presented to supplement the acceptable studies.

Apple (47248901.der.doc): Apple trees were treated with a single foliar application of [carbinol-^{14}C]flutriafol or [triazole-3,5-^{14}C]flutriafol during early fruit development at 0.11 lb ai/acre (1x/0.2x the proposed single/seasonal application rates). Samples of apple fruit (both labels) and foliage (triazole label only) were harvested at maturity, 64 days following application. Table B.1 is a summary of the total TRRs; TRRs were slightly higher in the triazole labeled samples.

The majority of the radioactivity (72-84% TRR) in apple fruit and foliage was solvent extracted with acetonitrile (ACN) and ACN/water. An additional ~5% TRR was released from apple fruit via mild acid (MA; 0.1 M HCl) and mild base (MB; 0.1 M NaOH) hydrolysis. Nonextractable residues were 18-23% TRR (≤0.012 ppm) in apple fruit and 16% TRR (0.685 ppm) in triazole-label foliage.

Residues were identified by high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) co-elution with reference standards (flutriafol, TA, TAA, and T). Total identified residues accounted for 50-56% of the TRR in apple fruit (Tables B.2 and B.3). Unknowns represented <5% TRR in fruit. Similar metabolic profiles were observed for the two labels.

Sugar beet (47090439.der.doc): Sugar beets were treated with a single foliar application of [carbinol-^{14}C]flutriafol or [triazole-3,5-^{14}C]flutriafol at ~0.12 lb ai/acre (BBCH 49; harvestable size root). Samples of sugar beet root and tops were collected 0, 6, 11, 16, and 21 days after treatment (DAT; 6- and 11-DAT samples were not analyzed). Table B.1 is a summary of the TRRs; TRRs did not vary with radiolabel position in sugar beet tops and TRRs in roots were to low to draw a conclusion (≤0.009 ppm; not analyzed further)

The majority of the radioactivity in sugar beet tops was solvent extracted with ACN and/or ACN/water (89-97% TRR). An additional ~3-4% TRR was released from 21-DAT tops via mild acid and base hydrolysis. Nonextractable residues were 5-11% TRR (0.029-0.078 ppm) in carbinol-label tops and 3-9% TRR (0.030-0.040 ppm) in triazole-label tops.

Residues were identified by HPLC and TLC co-elution with reference standards (flutriafol, TA, and TAA). HED notes that although TA and TAA were listed as reference standards, the behavior of these compounds under the employed analytical systems were not provided. A hexose conjugate of flutriafol was identified based on comparison of the study results with those of the rapeseed metabolism study. Total identified residues accounted for 73-95% TRR in sugar beet tops (Tables B.2 and B.3). Unknowns represented <8% TRR in tops. Similar metabolite profiles were observed for the two labels.

Rapeseed (47090438.der.doc): Rapeseed plants were treated with a single foliar application of [carbinol-^{14}C]flutriafol or [triazole-3,5-^{14}C]flutriafol at ~0.10 lb ai/acre (BBCH71; early pod set). Forage samples were harvested immediately following application; samples of pod and foliage were harvested 7 and 14 days after treatment (DAT); samples of whole plant were collected 21 DAT; and samples of foliage and seed were collected at maturity, 42 DAT. Samples harvested 7 and 21 DAT were not analyzed. Table B.1 is a summary of the TRRs; TRRs did not vary with radiolabel position.

The majority of the radioactivity (60-98% TRR) in forage/foliage was extracted by sequential extraction with ACN, ACN/water, and/or water; 40-41% TRR was extracted from 14-DAT pods with ACN/water. Mature seed was extracted with hexane (27-32% TRR) followed by ACN/water extraction (42% TRR). The following additional radioactivity was released via hydrolysis with enzyme (E; cellulase and hemicellulase), MA, MB, strong acid (SA; 6 M HCl), and strong base (SB; 2 M NaOH): 14- and 42-DAT foliage - combined 7-20% TRR; 14-DAT pods -combined 53% TRR; and 42-DAT seed - combined 14-22% TRR. Nonextractable residues were as follows: 14-DAT pods - 6-7% TRR in; 42-DAT seed - 4-7% TRR in; and forage/foliage - 1-11% TRR (≤0.034 ppm) except in 42-DAT carbinol-label foliage which had nonextractable residues of 20% TRR (0.071 ppm).

Residues were identified by HPLC and TLC co-elution with reference standards (flutriafol, TA, and TAA). HED notes that although TA and TAA were listed as reference standards, the behavior of these compounds under the employed analytical systems were not provided. Two metabolites, a hexose conjugate and a defluorinated flutriafol metabolite, were identified by LC/mass spectrometry (MS). Total identified residues accounted for 62-97% TRR in rapeseed forage, foliage, pods, and seed (Tables B.2 and B.3). Unknowns represented <8% TRR in forage, foliage, pods, and seeds. Similar metabolite profiles were observed for the two labels. Note that significant quantities of flutriafol were identified in the hydrolysates of 14-DAT pods (27-28% TRR) and 42-DAT foliage (3-11% TRR). Flutriafol was identified in the remaining hydrolysates at ≤7% TRR and defluorinated flutriafol was also identified in the hydrolysates at ≤15% TRR.

Barley/Wheat (foliar treatment; 47090440.der.doc): [Carbinol-^{14}C]flutriafol or [triazole-3,5-^{14}C]flutriafol were applied as a single foliar broadcast application to spring barley and spring wheat grown in pots maintained outdoors or in a greenhouse, at a rate of ~0.08 lb ai/acre. The applications were made 4-26 days prior to ear emergence, except for field-grown carbinol-label wheat and field-grown triazole-label barley in which applications were made after ear emergence. Samples of mature grain and straw were harvested 56-94 days after application for those samples treated pre-ear emergence and 44-45 days after application for those samples treated post-ear emergence. TRRs are summarized in Table B.1; TRRs did not vary significantly with label position for straw but varied with label position in grain with the triazole labeled yielding higher residues (chaff not analyzed further).

The majority of the radioactivity from the grain and straw samples (60-95% TRR; 47% TRR for field-grown triazole-label barley grain) was solvent extracted with ACN and ACN/water. Nonextractable residues accounted for 5-35% TRR (≤0.035 ppm) in the grain samples (both labels) and 16-40% TRR (0.150-0.336 ppm) in the straw samples (both labels). Nonextractable residues in triazole-label wheat straw (23% TRR) were subjected to limited sequential extraction procedures with cold and boiling water and cold 1 M ammonia (released an additional 7% TRR).

Residues were identified using TLC by co-elution or reference standards (flutriafol, TA, TAA, and triazole lactic acid). Total identified residues represented 36-38 % TRR in carbinol labeled grain and straw samples and 56-84% TRR in all triazole labeled grain and straw samples excluding the triazole-label field-grown barley grain sample treated post-ear emergence (32% TRR; Table B.4). Unknowns were ≤4% TRR in the carbinol labeled grain and straw samples, 5-14% TRR in the triazole straw samples, and 8-34% TRR in the triazole grain samples (sufficient characterization of these residues were performed). The metabolic profile did not vary significantly with label position in straw. However, the metabolic profile varied significantly with label position in grain samples due to the identification of TA and TAA in the triazole-label samples.

The following deficiencies were identified in the barley/wheat foliar metabolism study: (1) residues

in forage were not investigated; (2) insufficient attempts were made to characterize nonextractable residues of barley and wheat straw; (3) a confirmatory method was not used for the identification of metabolites; (4) the ACN/water barley straw extract (carbinol label) was not analyzed (20% TRR; 0.142 ppm), (5) no information concerning storage conditions or durations was provided, and (6) the GLP statement indicated that since Cheminova (the petitioner) did not conduct the study and was not the sponsor, they could not be certain that the study was conducted in accordance with GLP practices (40 CFR 160). In addition, supporting information and data were extremely limited for this study.

Barley/Wheat (seed treatment; 47090441.der.doc): Spring barley and spring wheat seed were treated with [carbinol-^{14}C]flutriafol or [triazole-^{14}C]flutriafol at a rate of 114 ppm and 104 ppm for carbinol-label barley and wheat, respectively, and 121 ppm and 73 ppm for triazole-label barley and wheat, respectively. Samples of barley and wheat grain, straw, and chaff were harvested 22 (barley commodities) or 16 (wheat commodities) weeks after planting (forage was not collected). TRRs are summarized in Table B.1. TRRs varied significantly with radiolabel position in grain and chaff with the triazole-label samples yielding higher TRRs (no variation in straw). Only the following samples were subjected to extraction and analysis procedures: barley straw (both labels) and triazole-label barley/wheat grain (carbinol grain samples were not analyzed due to low TRR (≤0.005 ppm)).

The majority of the radioactivity (84-88% TRR) in barley straw was solvent extracted with ACN and ACN/water. ACN released ≤1% TRR from triazole-label barley/wheat grain while ACN/water released 89-94% TRR. Nonextractable residues were 6-10% TRR (0.008-0.016 ppm) for triazole-label barley/wheat grain and 12-16% TRR (0.030-0.041 ppm) for triazole- and carbinol-label barley straw.

Residues were identified by TLC using co-ellution with reference standards (flutriafol, TA, TAA, and triazole propionic acid). Identified residues represented 72-83% TRR and 64% TRR in the triazole labeled grain and straw samples, respectively, and 59% TRR in the carbinol labeled straw sample (Table B.5). Unknowns were ≤5% TRR in the triazole labeled grain and straw samples and a combined 19% TRR (0.047 ppm) in the carbinol labeled straw sample. Significant differences in the metabolic profile were found in carbinol and triazole labeled grain and straw samples due to the identification of TA and TAA in the triazole-label samples.

The following deficiencies were identified in the barley and wheat seed treatment metabolism study: (1) residues in forage were not investigated, (2) a confirmatory method was not used for the identification of metabolites, (3) no information concerning storage durations was provided; and (4) the GLP statement indicated that since Cheminova (the petitioner) did not conduct the study and was not the sponsor, they could not be certain that the study was conducted in accordance with GLP practices (40 CFR 160). In addition, supporting information and data were extremely limited for this study.

Table B.1: TRRs

Crop	Timing and Applic. No.	PHI (days)	Matrix	TRR (ppm parent equivalents)[1]	
				Carbinol label	Triazole label
Foliar Plant metabolism Studies					
Apple	One foliar application made at early fruit development at 0.105 lb ai/acre	64	fruit	**0.041**	**0.065**
			foliage	not analyzed	**4.182**
Rapeseed	One foliar application made at early pod set at 0.105 lb ai/acre (carbinol label) or 0.103 lb ai/acre (triazole label)	0	Forage	**1.497**	**0.782**
		14	Pod	**0.779**	**0.751**
			Foliage	**1.601**	**1.165**
		42	Seed	**0.729**	**1.316**
			Mature Foliage	**0.355**	**0.246**
Sugar Beet	One foliar application made at the harvestable size root stage at 0.115 lb ai/acre (carbinol label) or 0.119 lb ai/acre (triazole label)	0	Root	<0.001	0.001
			Tops	**1.273**	**1.368**
		16	Root	0.005	0.003
			Tops	**0.381**	**0.342**
		21	Root	0.005	0.009
			Tops	**0.596**	**0.747**
Barley (field grown)	One foliar application made 13 days before ear emergence at 0.080 lb ai/acre.	62	grain	**0.007**	--
			straw	**0.72**	--
	One foliar application made after ear emergence at 0.075 lb ai/acre.	44	grain	--	**0.10**
			straw	--	0.12
Barley (greenhouse grown)	One foliar application made 26 days before ear emergence at ~0.080 lb ai/acre.	94	grain	0.02	**0.41**
			straw	not analyzed	**2.10**
Wheat (field grown)	One foliar application made after ear emergence at 0.079 lb ai/acre.	45	grain	0.006	--
			straw	0.53	--
	One foliar application made 20 days before ear emergence at 0.094 lb ai/acre.	74	grain	--	**0.05**
			straw	--	**0.65**
Wheat (greenhouse grown)	One foliar application made 4 days before ear emergence at ~0.080 lb ai/acre.	56	grain	0.01	**0.18**
			straw	not analyzed	not analyzed
Seed Treatment Metabolism Study					
Barley	Seed treatment at 114 ppm (carbinol label) or 121 ppm (triazole label).	154	grain	0.005	**0.17**
			straw	**0.25**	**0.24**
			chaff	0.06	0.21
Wheat	Seed treatment at 104 ppm (carbinol label) or 73 ppm (triazole label).	112	grain	0.003	**0.14**
			straw	0.17	0.23
			chaff	0.08	0.14

[1] Samples in bold were analyzed further.

Table B.2: Summary of Characterization and Identification of TRRs in Apple, Rapeseed, and Sugar Beet Following Foliar Application of [Carbinol-^{14}C]Flutriafol.

Compound	Apple		Rapeseed										Sugar Beet					
	64-DAT fruit TRR = 0.041 ppm		0-DAT forage TRR = 1.497 ppm		14-DAT Foliage TRR = 1.601 ppm		42-DAT Foliage TRR = 0.355 ppm		14-DAT Pod TRR = 0.779 ppm		42-DAT Seed TRR = 0.729 ppm		0-DAT Tops TRR = 1.273 ppm		16-DAT Tops TRR = 0.381 ppm		21-DAT Tops TRR = 0.596 ppm	
	% TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Flutriafol[1]	56.2	0.023	96.0	1.437	85.7	1.373	58.6	0.208	59.3	0.461	61.8	0.452	91.6	1.165	68.2	0.260	69.2	0.412
FHC (R5a)	--	--	0.5	0.007	2.7	0.043	2.5	0.009	1.7	0.013	3.8	0.028	0.1	0.001	4.4	0.017	3.8	0.023
DF (C6)	--	--	--	--	1.1	0.017	1.4	0.005	14.9	0.116	2.9	0.021	--	--	--	--	--	--
Unknown R1	--	--	--	--	--	--	4.5	0.016	--	--	--	--	0.2	0.002	5.3	0.020	2.6	0.016
Unknown R2	--	--	--	--	0.4	0.006	--	--	0.9	0.007	1.8	0.013	--	--	1.4	0.005	4.5	0.027
Unknown R3	--	--	--	--	0.9	0.015	0.6	0.002	1.5	0.012	1.6	0.012	--	--	1.4	0.005	2.5	0.014
Unknown R4	--	--	--	--	0.9	0.015	0.8	0.003	1.0	0.008	2.1	0.015	--	--	2.7	0.010	5.4	0.033
Unknown R5b	--	--	--	--	3.1	0.050	2.5	0.009	2.6	0.020	3.8	0.028	0.7	0.008	3.3	0.013	3.1	0.019
Unknown R6	--	--	0.9	0.013	0.6	0.010	0.6	0.002	--	--	--	--	0.7	0.008	0.7	0.003	0.8	0.005
Unknown C1	--	--	--	--	0.7	0.011	1.7	0.006	4.4	0.035	1.4	0.011	--	--	--	--	--	--
Unknown C2	--	--	--	--	0.1	0.001	--	--	0.4	0.003	--	--	--	--	--	--	--	--
Unknown C3	--	--	--	--	--	--	--	--	0.1	0.001	--	--	--	--	--	--	--	--
Unknown C4	--	--	--	--	0.1	0.001	--	--	0.4	0.003	--	--	--	--	--	--	--	--
Others (unknown)	8.8[3]	0.003	0.6	0.009	1.9	0.030	2.8	0.010	4.5	0.035	2.9	0.022	0.8	0.010	1.4	0.005	3.1	0.019
Unretained	0.8	<0.001	--	--	--	--	--	--	--	--	--		--	--	--	--	--	--
E[2]	not performed		not performed		3.3	0.053	4.0	0.014	16.3	0.127	1.3	0.009	not performed		not performed		not performed	
WA[2]	**2.4**	**0.001**			**0.2**	**0.003**	**0.6**	**0.002**	**0.5**	**0.004**	**0.3**	**0.002**					3.8	0.023
WB[2]	**2.6**	**0.001**			**0.4**	**0.006**	**1.1**	**0.004**	4.1	0.032	1.2	0.009						
SA[2]	not performed				1.5	0.024	11.4	0.040	18.5	0.144	8.8	0.064					not performed	
SB[2]					1.6	0.026	**2.4**	**0.009**	13.4	0.104	2.5	0.018						
Total identified	56.2	0.023	96.5	1.444	89.5	1.433	62.5	0.222	75.9	0.590	68.5	0.501	91.7	1.166	72.6	0.277	73.0	0.435
Total characterized	14.6	0.006	1.5	0.022	9.3	0.148	17.6	0.063	16.7	0.131	14.3	0.106	2.4	0.028	16.2	0.061	22.0	0.133
Total extractable	76.9	0.032	97.9	1.466	98.6	1.579	79.9	0.283	92.9	0.723	83.3	0.607	93.9	1.195	88.8	0.338	95.1	0.567
Unextractable	23.0	0.009	2.1	0.031	1.4	0.022	20.1	0.071	7.1	0.055	16.8	0.122	6.1	0.078	11.2	0.043	4.8	0.029
Accountability[4]	100		100		100		100		100		100		100		100		100	

[1] Includes flutriafol identified in the E, WA, WB, SA, and/or SB hydrolysates for 14-DAT rapeseed forage (E-2.8% TRR, SA-0.4% TRR,SB-0.7% TRR; total of 3.9% TRR;), 42-DAT rapeseed foliage (E-2.8% TRR and SA-8.2% TRR; total of 11.0% TRR), 14-DAT rapeseed pod (E-15.3% TRR, WB-3.3% TRR, SA-3.0% TRR, and SB-6.2% TRR; total of 28% TRR), 42-DAT rapeseed seed (E-0.4% TRR, WB-0.5% TRR, SA-4.9% TRR, and SB-1.5% TRR; total of 7% TRR), and 21-DAT sugar beet tops (combined WA and WB-1.9% TRR).

[2] Hydrolysates in bold were not analyzed.

[3] Largest unknown of 2.8% TRR.

[4] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis) * 100.

Table B.3: Summary of Characterization and Identification of TRRs in Apple, Rapeseed, and Sugar Beet Following foliar Application of [Triazole-^{14}C]Flutriafol.

Compound	Apple[1]		Rapeseed[1]								Sugar Beet					
	64-DAT Fruit		14-DAT Foliage		42-DAT Foliage		14-DAT Pod		42-DAT Seed		0-DAT Tops		16-DAT Tops		21-DAT Tops	
	TRR = 0.065 ppm		TRR = 1.165 ppm		TRR = 0.246 ppm		TRR = 0.751 ppm		TRR = 1.316 ppm		TRR = 1.368 ppm		TRR = 0.342 ppm		TRR = 0.747 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flutriafol[2]	49.9	0.032	82.7	0.963	55.6	0.137	59.4	0.446	67.6	0.889	95.4	1.304	77.7	0.266	70.8	0.529
FHC (R5a)[3]	--	--	2.7	0.031	5.7	0.014	1.5	0.011	3.8	0.050	--	--	1.1	0.004	5.0	0.038
DF (C6)	--	--	1.5	0.018	0.8	0.002	12.1	0.091	3.0	0.039	--	--	--	--	--	--
TA	<2	<0.001	--	--	--	--	--	--	--	--	--	--	--	--	--	--
TAA	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Unknown R1	--	--	0.3	0.003	4.9	0.012	1.6	0.012	3.5	0.046	0.2	0.003	8.1	0.028	3.1	0.023
Unknown R2	--	--	0.6	0.007	1.6	0.004	1.1	0.008	1.7	0.023	--	--	0.7	0.002	4.6	0.034
Unknown R3	--	--	1.2	0.014	1.2	0.003	0.8	0.006	--	--	--	--	0.9	0.003	2.1	0.016
Unknown R4	--	--	1.0	0.012	2.0	0.005	1.2	0.009	--	--	0.1	0.001	0.5	0.002	4.4	0.033
Unknown R5b	--	--	2.6	0.030	6.1	0.015	1.5	0.011	3.6	0.048	0.9	0.012	2.6	0.009	2.4	0.018
Unknown R6	--	--	0.3	0.003	--	--	--	--	--	--	0.2	0.003	--	--	1.0	0.008
Unknown C1	--	--	1.5	0.018	0.4	0.001	6.3	0.047	3.3	0.044	--	--	--	--	--	--
Unknown C2	--	--	0.1	0.001	--	--	0.5	0.004	--	--	--	--	--	--	--	--
Unknown C3	--	--	--	--	--	--	0.3	0.002	--	--	--	--	--	--	--	--
Unknown C4	--	--	0.1	0.001	--	--	0.5	0.004	--	--	--	--	--	--	--	--
Others (unknown)	21.6[3]	0.013	1.9	0.022	2.4	0.006	6.5	0.048	7.8	0.102	0.4	0.005	--	--	2.4	0.018
Unretained	2.0	0.001	--	--	--	--	--	--	--	--	--	--	--	--	--	--
E[4]	not performed		5.0	0.058	**2.6**	**0.006**	17.1	0.128	1.4	0.018	not performed		not performed		not performed	
WA[4]	**2.1**	**0.001**	**0.2**	**0.002**	**0.4**	**0.001**	**0.3**	**0.002**	**0.4**	**0.005**					3.8	0.023
WB[4]	**2.4**	**0.002**	**0.6**	**0.007**	**1.2**	**0.003**	2.8	0.021	3.0	0.039						
SA[4]	not performed		2.8	0.033	5.5	0.014	16.9	0.127	7.9	0.104					not performed	
SB[4]			2.8	0.033	**3.0**	**0.007**	15.8	0.119	9.1	0.120						
Total identified	49.9	0.032	86.9	1.012	62.1	0.153	73.0	0.548	74.4	0.978	95.4	1.304	78.8	0.270	75.8	0.567
Total characterized	28.1	0.017	10.4	0.120	25.8	0.063	21.0	0.156	21.4	0.282	1.8	0.024	12.8	0.044	20.0	0.150
Total extractable	82.2	0.054	97.0	1.130	88.9	0.218	94.1	0.706	95.8	1.26	97.1	1.328	91.1	0.312	95.8	0.716
Unextractable	17.8	0.012	2.9	0.034	11.1	0.027	5.8	0.044	4.3	0.057	2.9	0.040	8.9	0.030	4.2	0.031
Accountability[5]	100		100		100		100		100		100		100		100	

[1] Apple foliage and 0-DAT rapeseed forage were also analyzed but these data are not presented here (64-DAT apple foliage - 64-DAT; 4.182 ppm; 48% TRR flutrifol; 29% TRR unknowns; 16% TRR unextracted; 0-DAT rapeseed forage – 0.782 ppm; 97% TRR flutriafol).

[2] Includes flutriafol identified in the E, WA, WB, SA, and/or SB hydrolysates for 14-DAT rapeseed forage (E-4.5% TRR, SA-0.7% TRR, and SB-1.4% TRR; total of 6.6% TRR;), 42-DAT rapeseed foliage (SA-3.2% TRR; total of 3.2% TRR), 14-DAT rapeseed pod (E-15.8% TRR, WB-1.9% TRR, SA-3.2% TRR, and SB-6.1% TRR; total of 27% TRR), 42-DAT rapeseed seed (E-0.5% TRR, WB-0.8% TRR, SA-2.0% TRR, and SB-3.0% TRR; total of 6.3% TRR), and 21-DAT sugar beet tops (combined WA and WB-1.9% TRR).

[3] Largest unknown of 4.2% TRR.

[4] Hydrolysates in bold were not analyzed.

[5] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis) * 100.

Table B.4: Summary of Characterization and Identification of TRRs in Barley and Wheat Following Foliar Application of [Carbinol-^{14}C]- or [Triazole-^{14}C]-Flutriafol.

Compound	[Carbinol-^{14}C]-Flutriafol treated				[Triazole-^{14}C]-Flutriafol treated											
	Barley grain (62-DAT; field grown; treated pre-ear emergence)		Barley Straw (62-DAT; field grown; treated pre-ear emergence)		Wheat straw (74-DAT; field grown; treated pre-ear emergence)		Barley straw (94-DAT; greenhouse grown; treated pre-ear emergence)		Barley grain (44-DAT; field grown; treated after ear emergence)		Barley grain (94-DAT; greenhouse grown; treated pre-ear emergence)		Wheat grain (74-DAT; field grown; treated pre-ear emergence)		Wheat grain (56-DAT; greenhouse grown; treated pre-ear emergence)	
	TRR = 0.007 ppm		TRR = 0.72 ppm		TRR = 0.65 ppm		TRR = 2.10 ppm		TRR = 0.10		TRR = 0.41 ppm		TRR = 0.05 ppm		TRR = 0.18 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flutriafol	36.3	0.003	37.5	0.270	56.6	0.368	63	1.323	24.0	0.024	--	--	--	--	--	--
TA	--	--	--	--			--	--	7.6	0.008	40	0.164	57.9	0.029	48	0.086
TAA	--	--	--	--			--	--	--	--	26	0.107	26.4	0.013	8	0.014
Others (unknowns)	3.6	<0.001	2.9	0.021	13.6	0.088	5	0.105	7.9	0.008	21	0.086	9.9	0.005	34	0.061
Total identified	36.3	0.003	37.5	0.270	56.6	0.368	63	1.323	31.6	0.032	66	0.271	84.3	0.042	56	0.10
Total characterized	38.6	0.002	22.6	0.163	20.2	0.131	15	0.315	32.7	0.034	23.2	0.095	10.6	0.005	34	0.061
Total extractable	60.2[6]	0.005	60.2	0.434	73.8	0.480	81.0	1.701	47.4	0.048	89.2	0.366	94.9	0.047	90.0	0.162
Unextractable	25.7	0.002	39.8	0.287	23.1	0.150	16.0	0.336	35.1	0.035	6.5	0.027	5.1	0.003	5.0	0.009
Accountability[1]	86		100		97		97		83		96		100		95	

[1] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis) * 100.

Table B.5: Summary of Characterization and Identification of TRRs in Barley and Wheat Matrices Following Seed Treatment with [Carbinol-^{14}C]Flutriafol or [Triazole-^{14}C]Flutriafol at ~100 ppm.

Compound	Triazole label						Carbinol label	
	Barley grain TRR = 0.17 ppm		Wheat grain TRR = 0.14 ppm		Barley straw TRR = 0.24 ppm		Barley straw TRR = 0.25 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flutriafol	--	--	--	--	35.8	0.086	59.2	0.148
TA	36.4	0.062	55.2	0.077	--	--	--	--
TAA	35.2	0.060	27.8	0.039	28.0	0.067	--	--
Others (unknowns)	4.6	0.008	4.9	0.007	4.7	0.011	18.8	0.047
Total identified	71.6	0.122	83.0	0.116	63.8	0.153	59.2	0.148
Total characterized	12.3	0.021	5.3	0.008	4.7	0.011	18.8	0.047
Total extractable	90.3	0.154	94.4	0.133	87.7	0.211	83.7	0.209
Unextractable	9.7	0.016	5.7	0.008	12.3	0.030	16.4	0.041
Accountability[1]	100		100		100		100	

[1] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis) * 100.

Livestock Metabolism Studies: The petitioner submitted diary cow ([triazole-3,5-^{14}C]flutriafol) and hen ([triazole-3,5-^{14}C]flutriafol and [carbinol-^{14}C]flutriafol) metabolism studies. The following is a summary of these data.

Dairy Cow (47090443.der.doc): A single dairy cow was orally administered [triazole-3,5-^{14}C]flutriafol twice a day for seven consecutive days at a dietary rate of 2 ppm (10x). Milk was collected twice daily throughout the study and muscle, fat (subcutaneous, omental, and peritoneal), liver, and kidney were collected at sacrifice (4 hours after the final dose). Table B.6 is a summary of the TRRs. Radioactivity was highest in liver, and lowest in muscle and fat. Residues in milk were low (<0.01 ppm). The majority of the administered dose was excreted, with urine and feces accounting for ~78% of the administered dose.

The majority of the radioactivity was extracted with acetone/water from milk (97% TRR) and from liver and kidney with methanol (liver - 5% TRR; kidney - not performed), ACN/water (liver - 43% TRR; kidney - 81% TRR), and water (liver - 2% TRR; kidney - 8% TRR); muscle and fat were not extracted due to low TRRs (≤0.008 ppm). Bacterial protease hydrolysis of the unextracted liver residues released and additional 42% TRR. This hydrolysate was characterized further by partitioning with ether (ether – 0% TRR; water - 42% TRR) followed by hydrolysis of the aqueous phase with β-glucuronidase and 6M HCl with partitioning of the resulting hydrolysates with ether (ether phases – 0% TRR; aqueous phases - 42% TRR). The aqueous phase was then hydrolyzed with 0.1M NaOH and partitioned with ether (ether - 15% TRR (analyzed); aqueous phase - 18% TRR (not analyzed)). Nonextractable residues were 3-11% TRR (<0.03 ppm) in milk, kidney, and liver.

Residues were identified by TLC using co-elution with reference standards including flutriafol, four metabolites isolated from the rat metabolism study (M1B, M1D, M2B, and M2C), and a methoxyphenyl metabolite of flutriafol (Compound X). Reference standards for T, TA, and TAA were not included. Total identified residues accounted for <5-32% TRR in milk, kidney, and liver (Table B.7).

The following deficiencies were identified in the dairy cow metabolism study: (1) a confirmatory method was not used for the identification of metabolites; (2) no information concerning storage durations was provided; (3) reference standards for the triazole metabolites, T, TA, and TAA, were not included; and (4) the GLP statement indicated that since Cheminova (the petitioner) did not conduct the study and was not the sponsor, they could not be certain that the study was conducted in accordance with GLP practices (40 CFR 160). In addition, supporting information and data were extremely limited for this study.

Hen (47090442.der.doc): Laying hens were orally administered [triazole-3,5-^{14}C]flutriafol or [carbinol-^{14}C]flutriafol once a day for seven consecutive days at a dietary rate of 13.9 ppm (160x) or 11.6 ppm (130x), respectively. Eggs were collected twice daily throughout the study and muscle (composite of breast and thigh), abdominal fat, and liver were collected at sacrifice (20-24 hours after the final dose). Table B.6 is a summary of the TRRs. TRR were consistently higher in the triazole-label matrices. Radioactivity for both labels was highest in liver and lowest in muscle and fat. The majority (90-91%) of the administered dose was excreted.

The majority of the radioactivity was extracted from egg and muscle using ACN/water (64-98% TRR; both labels) and from fat using acetone/hexane (94-97% TRR; both labels). ACN/water extraction released lower levels of TRR from liver (33-41% TRR; both labels). Additional residues were released from liver (both labels) via sequential hydrolysis with pepsin and

pancreatin (21-25% TRR; analyzed), 1 N HCl (4-6% TRR; not analyzed), 1 M NH_4OH (8-9% TRR; not analyzed), and 6 N HCl at reflux (30% TRR carbinol label; 12% TRR triazole label; not analyzed). Nonextractable residues (both labels) accounted for 2.4-6.0% TRR (0.004-0.008 ppm) in eggs, 6.3-36.4% TRR (0.004 ppm) in muscle, 2.9-6.3% TRR in fat (0.001 ppm), and 1.4-8.5% TRR (0.005-0.035 ppm) in liver.

Residues were identified by HPLC and TLC using co-elution with reference standards (flutriafol, T, TA, and TAA). Approximately 73-94% of the TRR was identified in eggs and fat from both labels (Table B.8). In muscle and liver, significant differences were observed in identified residues between the labels (muscle/liver - 9%/4% TRR in carbinol-label -vs- 77%/21% TRR in triazole-label). Unknowns M3 (≤45% TRR) and M4 (≤7% TRR) were identified in several of the matrices. Attempts to further characterize M3 and M4 by preparative HPLC and acid and base hydrolysis indicated that M4 was partially hydrolyzed via acid hydrolysis to yield a product with an HPLC retention time between that of the hydroxylated flutriafols and flutriafol. Metabolite M3 was not significantly hydrolyzed under acid conditions, but did show some decomposition on base hydrolysis. Metabolite M3 was the major metabolite detected in carbinol-label muscle at 46% TRR (0.005 ppm) and was present in triazole-label muscle at 9% TRR. Minor components, grouped as "other unknowns" accounted for ≤5% TRR in eggs, ≤9% TRR in muscle, 3% TRR in triazole-label fat, and 10-12% TRR (0.043-0.045 ppm) in liver. Significantly different metabolic profiles were observed in the triazole and carbinol labeled samples due to the identification of T in all of the triazole samples or M3 in the carbinol muscle sample.

Table B.6: TRRs in Milk, Tissue and Excreta Following Dosing with [Triazole-3,5-^{14}C]Flutriafol or [Carbinol-^{14}C]Flutriafol.

Matrix	Collection Timing	[Triazole-3,5-^{14}C]Flutriafol (ppm)		[Carbinol-^{14}C]Flutriafol (ppm)	
		Diary Cow	Hen[1]	Dairy Cow	Hen[1]
Milk/Egg	Day 1 am	--	--	Dosing with [Carbinol-^{14}C]Flutriafol was not performed.	--
	Day 1 pm	0.002	0.001		No sample
	Day 2 pm	0.004	0.041		0.032
	Day 2 am	0.005	0.089		0.016
	Day 3 pm	0.006	0.088		0.051
	Day 3 am	0.006	0.135		No sample
	Day 4 pm	0.007	0.129		0.079
	Day 4 am	0.007	No sample		0.116
	Day 5 pm	0.007	0.145		0.101
	Day 5 am	0.007	0.184		No sample
	Day 6 pm	0.008	0.167		0.117
	Day 6 am	0.007	0.206 (0.205)		0.160 (0.159)
	Day 7 pm	0.008	0.190		0.126
	Day 7 am	0.007	0.204		0.121
	Day 8 am	--	0.184 (0.204)		0.133 (0.134)
Muscle	At sacrifice	0.008	0.060 (0.064)		0.011 (0.011)
Fat	At sacrifice	--	0.038 (0.035)		0.018 (0.016)
Fat, subcutaneous	At sacrifice	0.002	--		--
Fat, omental	At sacrifice	<0.001	--		--
Fat, perirenal	At sacrifice	0.003	--		--
Kidney	At sacrifice	0.061	--		--
Liver	At sacrifice	0.291	0.360 (0.411)		0.343 (0.359)
Heart	At sacrifice	0.011	--		--

[1] TRR reported in parentheses were calculated by summing extractable and nonextractable radioactivity.

Table B.7: Summary of Characterization and Identification of Radioactive Residues in Cow Matrices when Dosed with [Triazole-3,5-^{14}C]Flutriafol at 2 ppm in the Diet.

Compound	Milk TRR = 0.008 ppm		Kidney TRR= 0.061 ppm		Liver TRR= 0.291 ppm	
	% TRR	ppm	% TRR	ppm	%TRR	ppm
Flutriafol	1	<0.001	7	0.004	29	0.084
4-Hydroxyflutriafol (M1B)	<4	<0.001	<23	<0.014	1	0.003
4-Hydroxy-5-methoxyflutriafol (M1D)	--	--	--	--	2	0.006
Enzyme solubilzed	--	--	--	--	42[1]	0.122
Total identified	<5	<0.001	<30	<0.018	32	0.093
Total characterized	38	0.003	34	0.021	51	0.148
Total extractable	97	0.008	89	0.054	92	0.268
Unextractable	3	<0.001	11	0.007	9	0.026
Accountability[2]	100		100		101	

[1] The hydrolysate was further characterized via sequential hydrolysis followed with ß-glucuronidase, 6M HCl, and 0.1 M NaOH with ether partitioning between each hydrolysis. The TLC of the ether fractions detected flutriafol, M1D and unknowns ("each at <10% TRR", but no quantitative data were reported), the aqueous phase was not chromatographically analyzed and contained 18% TRR (0.052 ppm).

[2] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis) * 100.

Table B.8: Summary of Characterization/Identification of TRRs Hen Matrices Dosed with [Triazole-3,5-^{14}C]Flutriafol or [Carbinol-^{14}C]Flutriafol in the Diet.

Compound	[Carbinol-^{14}C]Flutriafol at 11.6 ppm in the Diet										[Triazole-3,5-^{14}C]Flutriafol at 13.9 ppm in the Diet									
	Eggs Day 6		Eggs Day 8		Muscle		Fat		Liver		Eggs Day 6		Eggs Day 8		Muscle		Fat		Liver	
	TRR= 0.159 ppm		TRR = 0.134 ppm		TRR= 0.011 ppm		TRR= 0.016 ppm		TRR= 0.359 ppm		TRR= 0.205 ppm		TRR = 0.204 ppm		TRR= 0.064 ppm		TRR= 0.035 ppm		TRR= 0.411 ppm	
	% TRR	ppm	%TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	%TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flutriafol	74.8	0.119	65.7	0.088	--	--	75.0	0.012	1.9	0.007	48.3	0.099	50.5	0.103	--	--	80.0	0.028	3.2	0.013
T	--	--	--	--	--	--	--	--	--	--	29.3	0.060	27.5	0.056	75.0	0.048	11.4	0.004	16.6[5]	0.068
Hydroxylated flutriafols (M5)	5.7	0.009	7.5	0.010	9.1	0.001	--	--	1.9	0.007	4.4	0.009	4.4	0.009	1.6	0.001	2.9	0.001	1.5	0.006
Unknown M3	13.2	0.021	12.7	0.017	45.5	0.005	6.3	0.001	7.0	0.025	8.8	0.018	11.3	0.023	9.4	0.006	2.9	0.001	6.6	0.027
Unknown M4	3.1	0.005	3.7	0.005	--	--	--	--	7.0	0.025	1.5	0.003	2.9	0.006	--	--	--	--	5.8	0.024
Unknown M2	--	--	--	--	--	--	--	--	2.5	0.009	--	--	--	--	--	--	--	--	--	--
Other unknowns	0.5	0.001	4.5	0.006	9.1	0.001	--	--	12.5	0.045	5.4	0.011	0.5	0.001	7.8	0.005	2.9	0.001	10.5	0.043
Oily phase	--	--	--	--	--	--	5.0	0.001	--	--	--	--	--	--	--	--	3.0	0.001	--	--
Enzyme hydrolysate –DCM phase	not performed								4.5[3]	0.016	not performed								5.4	0.022
Enzyme hydrolysate –aqueous phase									16.7[3]	0.060									17.1[6]	0.070
1N HCl hydrolysate									5.8[4]	0.021									4.1[4]	0.017
1M NH_4OH hydrolysate									8.1[4]	0.029									8.8[4]	0.036
6N HCl hydrolysate – DCM phase									5.3[4]	0.019									0.7[4]	0.003
6N HCl hydrolysate – aqueous phase									25.1[4]	0.090									11.2[4]	0.046
Total identified	80.5	0.128	73.2	0.018	9.1	0.001	75.0	0.012	3.8	0.014	82.0	0.168	82.4	0.168	76.6	0.049	94.3	0.033	21.3	0.087
Total characterized	16.9	0.027	20.9	0.028	54.6	0.006	11.3	0.002	94.5	0.339	15.7	0.032	14.7	0.030	17.2	0.011	8.8	0.003	70.2	0.288
Total extractable	97.5	0.155	94.0	0.126	63.6	0.007	93.8	0.015	98.6	0.354	97.6	0.200	97.1	0.198	93.8	0.060	97.1	0.034	91.5	0.376
Unextractable [1]	2.5	0.004	6.0	0.008	36.4	0.004	6.3	0.001	1.4	0.005	2.4	0.005	2.9	0.006	6.3	0.004	2.9	0.001	8.5	0.035
Accountability[2]	99		101		100		89		105		100		111		107		92		114	

[1] Residues remaining after exhaustive extractions.

[2] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis) * 100.

[3] The DCM phase of the enzyme hydrolysate was analyzed by TLC (nothing identified) and aqueous phase was analyzed by HPLC (nothing identified).

[4] These hydrolysates were not analyzed further.

[5] 2.7% TRR found in the enzyme hydrolysate.

[6] The DCM phase of the enzyme hydrolysate was analyzed by TLC (unknowns ≤2.9% TRR; ≤0.012 ppm) and aqueous phase was analyzed by HPLC.

Confined Rotational Crop Study: [Carbinol-^{14}C]flutriafol or [triazole-3,5-^{14}C]flutriafol was incorporated into bare loam soil at a target rate of 0.22 lb ai/acre (1x the proposed rate for soybean; 47090451.der.doc). Rotational crops of wheat, pea, sugar beet, and rapeseed were planted 30, 120, and 365 days after soil treatment and maintained in a greenhouse. Samples of wheat (grain, straw, and chaff), pea (seed, pod, and foliage), sugar beet (root and top), and rapeseed (seed, pod, and foliage) were harvested at maturity. Table B.9 is a summary of the TRRs in the harvested samples (30-day plantback interval (PBI) rapeseed samples were not analyzed). TRRs were generally higher in the triazole-label matrices than in the carbinol-label matrices and were lowest at the 365-day PBI.

TRR in all rotated matrices were initially determined in 1981/1983. TRR were determined in 1987 for the following samples chosen for further investigations: carbinol label - 120-day wheat straw and sugar beet tops; triazole label - 120- and 365-day wheat grain/straw and 120-day sugar beet top/root. The subject samples were extracted with ACN and ACN/water. The distribution of radioactivity into the extracts was not reported. Nonextractable residues accounted for <10% TRR or ≤0.05 ppm in all analyzed matrices excluding the following: carbinol label - 120-day wheat straw (18% TRR; 0.196 ppm); triazole label - 120-day wheat grain (13% TRR; 0.150 ppm) and 120-day wheat straw (17% TRR; 0.419 ppm).

Based on the general extraction flowchart provided in the study, the extracts were TLC analyzed. However, no details of the system were provided and the method of metabolite identification was not described (no reference standards were listed). Identified residues accounted for 26-43% TRR in the carbinol labeled samples and 43-67% TRR in the triazole labeled samples (Table B.10). The metabolic profile varied with radiolabel position due to the identification of T, TA, and/or TAA in the triazole labeled samples.

The following deficiencies were identified in the confined rotational crop study: (1) the study did not include a leafy vegetable crop; (2) residues in wheat forage were not investigated; (3) sandy loam soil was not used and no data were provided concerning the soil characteristics; (4) insufficient information was provided concerning analytical methodology and a confirmatory method was not used for the identification of metabolites; (5) insufficient information was provided to determine whether identification/characterization of residues met Agency requirements (e.g., five unknowns designated "others" accounted for up to >50% of TRR in carbinol-label sugar beet tops and were not further investigated; reference standards used not identified); (6) insufficient attempts were made to characterize nonextractable residues of 120-day wheat straw and grain and 365-day wheat straw samples; (7) insufficient storage stability data/information are available to support the storage interval of at least 4 years; and (8) insufficient information/data in general were provided to support the study, including details of sample handling at the field site and analytical laboratory; the distribution of radioactivity into sample extracts and fractions; representative chromatograms, raw data, or example calculations; and storage conditions and durations.

Table B.9: TRR in Rotated Crop Matrices.[1]				
Crop	Matrix	Plantback interval (days)	[carbinol-^{14}C]flutriafol ppm	[triazole-3,5-^{14}C]flutriafol ppm
Wheat	Grain	30	0.04	1.04
		120	0.02	**1.22 (1.18)**
		365	<0.01	0.3 (0.31)
	Straw	30	10.46	6.47
		120	**0.93 (1.07)**	**1.32 (2.45)**
		365	0.13	**0.2 (0.16)**
	Chaff	30	2.90	1.82
		120	0.88	1.58
		365	0.10	0.2
Pea	Seed	30	0.01	0.32
		120	<0.01	0.32
		365	<0.01	0.2
	Pod	30	0.05	0.14
		120	0.03	0.10
		365	<0.01	0.1
	Foliage	30	1.25	1.08
		120	0.33	0.63
		365	<0.01	0.1
Sugar beet	Root	30	0.02	0.08
		120	<0.01	**0.09 (0.12)**
		365	<0.01	0.03
	Tops	30	0.20	0.60
		120	**0.19 (0.31)**	**0.57 (0.56)**
		365	0.13	0.35
Rapeseed	Seed	30	Not determined	
		120	0.03	2.16
		365	<0.01	0.6
	Pod	30	Not determined	
		120	0.97	2.13
		365	0.13	0.3
	Foliage	30	Not determined	
		120	0.28	0.67
		365	0.04	0.1

[1] TRR were initially determined in 1981/1983; TRR re-determined in 1987 are presented in parentheses; only those samples in bold were analyzed further.

Table B.10: Summary of Characterization/Identification of TRRs in Rotational Crop Samples Following Soil Treatment with [Triazole-3,5-^{14}C]Flutriafol or [Carbinol-^{14}C]Flutriafol.

Compound	[Carbinol-^{14}C]Flutriafol				[Triazole-3,5-^{14}C]Flutriafol											
	Sugar beet top 120-day		Wheat straw 120-day		Sugar beet root 120-day		Sugar beet top 120-day		Wheat grain 120-day		Wheat grain 365-day		Wheat straw 120-day		Wheat straw 365-day	
	TRR = 0.31 ppm		TRR = 1.07 ppm		TRR = 0.12 ppm		TRR = 0.56 ppm		TRR = 1.18 ppm		TRR = 0.31 ppm		TRR = 2.45 ppm		TRR = 0.16 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flutriafol	25.7	0.080	43.3	0.463	4.3	0.005	17.0	0.095	--	--	--	--	38.2	0.936	30.7	0.049
4-hydroxy flutriafol	--	--	--	--	--	--	2.5	0.014	--	--	--	--	1.5	0.037	--	--
TA	--	--	--	--	19.6	0.024	2.5	0.014	48.5	0.572	50.5	0.157	--	--	1.1	0.002
TAA	--	--	--	--	2.7	0.003	21.0	0.118	18.8	0.222	14.2	0.044	15.5	0.380	22.2	0.036
T	--	--	--	--	17.3	0.021	--	--	--	--	--	--	--	--	--	--
Others[1]	51.2	0.159	25.5	0.273	--	--	15.9	0.089	--	--	--	--	16.8	0.412	3.0	0.005
Baseline	--	--	0.7	0.007	4.7	0.006	1.4	0.008	--	--	--	--	--	--	--	--
Remainder	0.5	0.002	1.8	0.019	2.6	0.003	0.5	0.003	4.8	0.057	0.6	0.002	5.5	0.135	3.5	0.006
Total identified	25.7	0.080	43.3	0.463	43.9	0.053	43	0.241	67.3	0.794	64.7	0.201	55.2	1.353	54.0	0.087
Total characterized	51.2	0.161	28.0	0.299	7.3	0.009	15.9	0.100	4.8	0.057	0.6	0.002	22.3	0.547	6.5	0.011
Total extractable[2]	77.4	0.241	71.3	0.762	51.2	0.062	60.8	0.341	72.1	0.851	65.3	0.203	77.5	1.900	60.5	0.098
Unextractable[3]	7.0	0.022	18.3	0.196	35.6	0.043	3.6	0.020	12.7	0.150	15.2	0.047	17.1	0.419	31.4	0.050
Accountability[4]	84.8 (138)		90 (103)		88 (117)		64 (63)		84.8 (82.0)		80.6 (83.3)		94.7 (176)		92.5 (74.0)	

[1] Consisting of at least 5 compounds in carbinol-label sugar beet tops , 3 compounds in carbinol-label wheat straw, 2 compounds in 120-day triazole-label wheat straw, an unspecified number of compounds in 365-day triazole-label wheat straw, and 2 compounds in triazole-label sugar beet tops.

[2] Total identified and characterized residues; actual extraction distributions were not reported.

[3] Residues remaining after extraction.

[4] Accountability = (Total extractable + Total unextractable)/(TRR) * 100; values in parentheses are calculated using the initial TRR from 1981/1983.

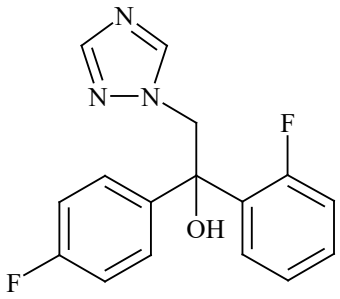
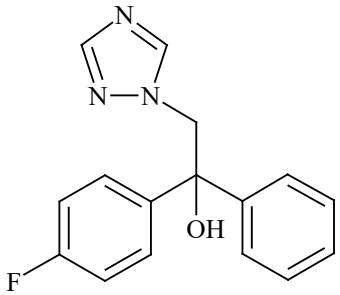
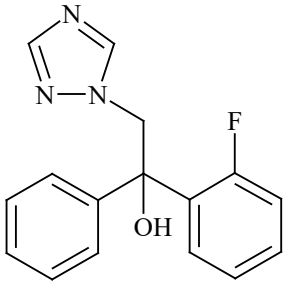
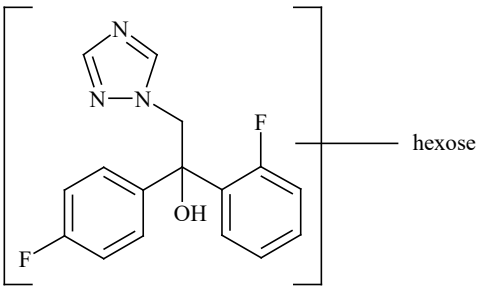
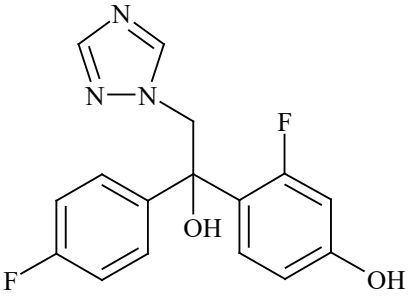
Appendix C. Tolerance Summary Table

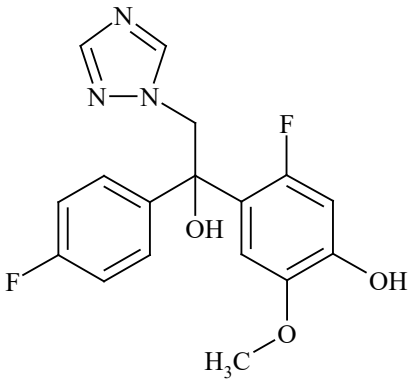
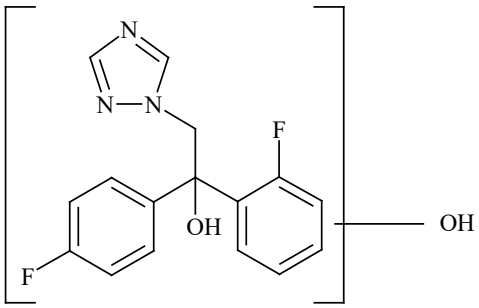
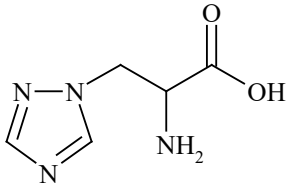
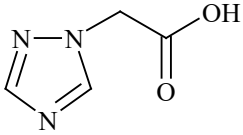
HED has determined that the terminal residue of concern in apple and soybean seed, for purposes of tolerance enforcement, is flutriafol *per se*. The tolerance expression proposed in this petition is appropriate (note that the flutriafol chemical name in 40 CFR 180.629 should be changed to the CAS chemical name: (±)-α-(2-fluorophenyl)-α-(4-fluorophenyl)-1*H*-1,2,4-triazole-1-ethanol). No Codex, Canadian, or Mexican MRLs have been established for flutriafol (see attachment 1). Therefore harmonization is not an issue for this petition. The proposed tolerances should be revised to reflect the correct commodity definition and/or numerical tolerance specified in Table C.1. A revised Section F is requested

Table C.1: Tolerance Summary for Flutriafol.

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Apple	0.2	0.20	Numerical tolerance should be 0.20.
Soybean	0.3	0.35	Based on the field trial data and the tolerance calculator, the numerical tolerance should be 0.35 ppm and the correct commodity definition is "Soybean, seed."
Soybean, aspirated grain fractions	0.5	2.2	Based on the field trial and processing data, the numerical tolerance should be 2.2 ppm and the correct commodity definition is "Grain, aspirated fractions."
Liver (cattle, goat, hog, horse, sheep)	0.01	--	Incorrect commodity definition.
Cattle, liver	--	0.02	--
Goat, liver	--	0.02	--
Hog, liver	--	0.02	--
Horse, liver	--	0.02	--
Sheep, liver	--	0.02	--
Eggs	0.01	--	Tolerance not required.

Appendix D: Chemical Name and Structure Table

Common name; Company code	Chemical name	Chemical structure
Flutriafol	(*RS*)-2,4'-difluoro-α-(1*H*-1,2,4-triazol-1-ylmethyl)benzhydril alcohol	
Defluorinated flutriafol/C6	Not provided	 or 
Flutriafol hexose conjugate/R5a	Not provided	
4-hydroxyflutriafol/M1B	1-(2-fluoro-4-hydroxyphenyl)-1-(4-fluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol	

Common name; Company code	Chemical name	Chemical structure
4-hydroxy-5-methoxyflutriafol/M1D	1-(2-fluoro-4-hydroxy-5-methoxyphenyl)-1-(4-fluorophenyl)-2-(1*H*-1,2,4-triazol-1yl)ethanol	
Monohydroxy flutriafol derivatives/M5	Not provided	
Triazolylalanine (TA)	2-amino-3-(1*H*-1,2,4-triazol-1-yl)propanoic acid	
Triazolylacetic acid (TAA)	1*H*-1,2,4-triazol-1-ylacetic acid	
1,2,4-Triazole (T)	1*H*-1,2,4-triazole